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‘That Time of the Month’ – Investigating the Influence of the Menstrual Cycle and Oral Contraceptives on the Brain Using Magnetic Resonance Imaging

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ABSTRACT

The stereotypic and oversimplified relationship between female sex hormones and undesirable behavior dates to the earliest days of human society, as already the ancient Greek word for the uterus, “hystera” indicated an aversive connection. Remaining and evolving throughout the centuries, transcending across cultures and various aspects of everyday life, its perception was only recently reframed. Contemporarily, the complex interaction of hormonal phases (i. e., the menstrual cycle), hormonal medication (i. e., oral contraceptives), women’s psychological well-being, and behavior is the subject of multifaceted and more reflected discussions. A driving force of this ongoing paradigm shift was the introduction of this highly interesting and important topic into the realm of scientific research. This refers to neuroscientific research as it enables a multimodal approach combining aspects of physiology, medicine, and psychology. Here a growing body of literature points towards significant alterations of both brain function, such as lateralization of cognitive functions, and structure, such as gray matter concentrations, due to fluctuations and changes in hormonal levels. This especially concerns female sex hormones. However, the more research is conducted within this field, the less reliable these observations and derived insights appear. This may be due to two particular factors: measurement inconsistencies and diverse hormonal phases accompanied by interindividual differences. The first factor refers to the prominent unreliability of one of the primarily utilized neuroscientific research instruments: functional magnetic resonance imaging (fMRI). This unreliability is seemingly present in paradigms and analyses, and their interplay, and is additionally affected by the second factor. In more detail, hormonal phases and levels further influence neuroscientific results obtained through fMRI as outcomes vary drastically across different cycle phases and medication. This resulting vast uncertainty thus tremendously hinders the further advancement of our understanding of how female sex hormones might alter brain structure and function and, ultimately, behavior.
This review summarizes parts of the current state of research and outlines the essential requirements to further investigate and understand the female brain’s underlying physiological and anatomical features.

‘You’re in such a bad mood. Is it that time of the month again?’ Biologically healthy females in their reproductive years are likely to be confronted with such statements at ‘that time of the month’, the beginning of the period and the start of a new menstrual cycle.

The earliest records reveal that the menstrual cycle affects mood and behavior in women and thus the central operation system, the brain. Plato suspected that the mourning womb, grieving over not carrying a child, might cause the monthly experienced symptoms

[1]; the ancient Greeks named the uterus after a behavioral trait probably caused by this organ, which was only discovered in women – hystera. These popular expressions are not unsubstantiated. Scientific studies proved that some women do experience an increase in anxiety around their menstruation [2] and the menstrual cycle; the intake of 'the pill', also affects the structure and function of the brain (for a general overview, please see, e. g. [3–5]). However, precise theories of how menstrual cycle phases and the intake of hormonal contraceptives influence and shape the human brain is yet limited. It is precisely this question that neuroscientists have been dealing with for more than 20 years.

To better understand the effect of sex hormones, particularly the key players of the menstrual cycle, estradiol and progesterone, on the brain, one must first understand their underlying modes of action, beginning with the binding to their specific receptors. One must distinguish between four naturally biosynthesized estrogens in women, focusing on estrogens. Estrone (E1) is predominant during menopause and is the weakest in effect, whereas estradiol (E2) shows the most potent effects and is present during the menstrual cycle before pregnancy and menopause. Estriol (E3) is the predominant estrogen during pregnancy, and estetrol (E4) is also only present during pregnancy [6]. Estrogens exert their effects after binding to one of two to date known distinct intracellular estrogen receptors (ER): estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). ERs are steroid receptors and act as ligand activation transcription factors, resulting in the modulation of gene transcription [7]. ERα and ERβ are vastly distributed in the brain, whereas both receptors have overlapping expression patterns in most parts of the human brain. Both receptors are present in the cerebral cortex but with different concentration patterns in distinct cortical layers. Whereas ERα expression dominates in the hypothalamus and the amygdala with only a low accumulation of ERβ, the opposite applies to the entorhinal cortex, thalamus, and hippocampal regions, which are one of the most abundant ERβ expressing areas [8]. This distinct expression of both receptors assigns particular roles to both receptor types, with ERα being involved in the modulation of neuronal populations with autonomic and reproductive neuroendocrine functions, emotional processing, affective and motivational behaviors, and ERβ modulating cognition, non-emotional memory, and motor functions. Additionally, estrogens, particularly estradiol, provide neuroprotective effects in the central nervous system due to attenuation of neuroinflammation and neurodegeneration [6].

Progesterone (P_4) is another sex hormone associated with neuroprotective effects, besides its well-studied role in regulating reproduction and female sexual behaviors. Additionally, in its role as a neurosteroid, it is involved in neuroplasticity [9], neurogenesis [10], and neuroinflammation [11]. Because of its diverse effects, it is not surprising that progesterone receptors are broadly expressed throughout the brain.

The role of progesterone in the brain regarding cognitive brain functions was already discussed 20 years ago. Hausmann and Güntürkün (2000) described the effect of progesterone on brain lateralization of cognitive functions and postulated the *progesterone mediated interhemispheric decoupling hypothesis* [12].

The general concept of the lateralization of cognitive function to either one of the two hemispheres is a basic principle of the organization of the human brain. Different cognitive functions, e. g., language, spatial attention, face processing, and memory, are distributed differently across the brain's two hemispheres, known as hemispheric specialization. With the advent of the development of modern brain imaging techniques, in particular functional transcranial Doppler sonography (fTCD) and fMRI, the study of the hemispheres of the brain is more widely feasible and has enabled non-invasive studies addressing the issue of the hemispheric specialization of cognitive functions in large cohorts of healthy participants as well as patients [13]. The current method of choice for measuring brain function is fMRI, as it is non-invasive and without any known side effects.

With the advent of these improvements in methodology, researchers could show that various cognitive functions are mainly located in one hemisphere; for example, in most individuals, language functions are lateralized to the left hemisphere [14–16]. In contrast, visuospatial functions are processed by the right hemisphere [17, 18]. However, these studies also highlighted that for all these processes, the degree of lateralization is variable not only between subjects but also within subjects. For example, language, as a typically left-hemispheric localized cognitive function, an atypical right-hemispheric or bilateral form of language lateralization has been observed in up to 10 % of the human population [14, 19–22]. Visuospatial attention function, a predominantly right-hemispheric cognitive function, is again subject to marked variability across subjects [17, 23–25].

Besides the hemispheric specialization of various cognitive tasks, these functions, especially language and visuospatial processes, have also been shown to be lateralized to a sex-specific manner. These studies found more pronounced functional cerebral asymmetries (FCAs) in men than women [26, 27] and consequently highlight the role of sex hormones for inter- and intraindividual variations in FCAs. In general, FCAs are a simple model to investigate functional connectivity in the brain, especially between the left and right cerebral hemispheres, referring to the relative differences in many neural functions and cognitive processes [28–31]. FCAs tend to be stable and more robust in men, whereas they greatly vary in women with an overall more symmetrical or bilateral pattern [12, 26]. However, this is not the case over women's entire lifespan. After menopause and during menses, FCAs are comparable to those in men, highlighting the role of gonadal hormones, especially progesterone, in modulating lateralization patterns, leading us back to the progesterone-mediated interhemispheric decoupling hypothesis. Hausmann and Güntürkün (2000) examined the effect of gonadal hormones on FCAs and concluded that FCAs seem to be hormonally modulated by a global mechanism: In general, both hemispheres work as partially independent systems, with each processing stimuli simultaneously. Such simultaneous and independent processing requires control mechanisms to coordinate and control the outputs from both hemispheres [12]. One coordinating key mechanism is the interhemispheric inhibition across the corpus callosum, which determines FCAs [32]. The corpus callosum consists of large parts of excitatory glutamatergic pyramidal neurons' fibers and only a small amount of inhibitory gamma-Aminobutyric acid-ergig (GABAergig) fibers [33]. Although the amount might be smaller, the longer-lasting effects of callosal activation are inhibitory and can be induced pharmacologically, resulting in

an attenuation of non- *N*-methyl-D-aspartate receptor (non-NMDA) glutamate receptors and a reduction of short excitatory and longer-lasting inhibitory influence [34].

The same effects are revealed by physiological doses of progesterone [35]. Thus, as they occur naturally during the luteal phase of the menstrual cycle, high progesterone levels can reduce transcallosal inhibition and thus lead to a functional decoupling of the hemispheres and hence a temporary reduction of FCAs. In summary, this leads to an overall functional hemispheric decoupling and, thus, to a temporal decrease in functional asymmetry. The authors conclude that steroid fluctuations during the menstrual cycle modify cerebral asymmetries to a certain extent, with the decrease in sex hormones (during menses and after menopause), stabilizing cerebral asymmetries, and an increase (during the midluteal phase), leading to reduced lateralization. Even more interesting, during low hormonal phases (menstruation), female asymmetries are similar to that of men and post-menopausal women.

Whereas the described hypothesis is 20 years old, it has received some empirical support from different studies with various designs and techniques [28, 29, 36].

For example, Pletzer and colleagues compared behavioral performance using a Navon figure paradigm. They investigated men, naturally cycling women with women during the follicular and during the luteal phase, and users of oral contraceptives (OCs) during the active pill phase [37]. During the focused attention condition, luteal women showed reduced global advantage displayed by faster responses to global vs. local targets compared to men, follicular women, and OC users. This is underpinned by sex hormone concentration as a global advantage during the focused attention condition related significantly positively to testosterone levels and significantly negatively to progesterone, but not estradiol levels. Further, interference was significantly enhanced in OC users as compared to women with a menstrual cycle and related positively to testosterone levels in all naturally cycling women and men. Highly interestingly, when each group was separately analyzed, the relationship of testosterone to global advantage and interference was reversed in women during their luteal phase as opposed to men and women during their follicular phase. These results support the hypothesis of progesterone-mediated inter-hemispheric decoupling, as global processing is lateralized to the right and local processing to the left hemisphere. Additionally, the obtained effects might result from a testosterone-mediated enhancement of right-hemispheric functioning.

In a combined behavioral and MRI study, behavioral results and MRI activation patterns were compared in naturally cycling women, women taking OCs, and men. Subjects performed two distinct numerical tasks. They reported that OC-users resemble follicular women in their behavioral performance but show male-like brain activation patterns during both tasks [38].

A more recent fTCD study underlined the results and reported lower test-retest reliability in women taking oral contraceptives (OC) compared to men investigating language dominance. Interestingly, the included women showed a significant shift from left hemisphere dominance towards bilaterality around menstruation with a significant reversal afterward. Authors declared the menstrual cycle a source of inconsistency and a challenge for language dominance assessment in epilepsy [39].

A newly developing research area is the effect of menstrual cycle phases on the resting state [40]. In addition to task-related functional brain imaging studies, these studies revealed several functionally relevant cortical networks that exhibit synchronous fluctuations in brain activity while participants are at rest without performing a specific task. Resting-state fMRI (RS fMRI) has identified specific networks that are spatially comparable to task-related activations, for example, the default mode network (DMN), which is comprised of the dorsal and ventral medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC)/precuneus and lateral parietal cortex [41–43]. Whereas the function of this network was hypothesized to be stimulus-independent, reflecting the brain activity, e. g., during daydreaming or mind-wandering [44], more recently, it has been suggested that RS activity in this network reflects spontaneous, intrinsic brain activity [45].

To date, only a few studies have investigated sex hormonal effects on RS connectivity displaying a significant heterogeneity in terms of methodology and obtained results. Petersen et al. (2014) applied a between-subjects design to investigate RS connectivity in the anterior part of the DMN under different hormonal states, both across the menstrual cycle in normally cycling women and in oral contraceptive pill users. This study reported increased RS connectivity between the right anterior cingulate cortex (ACC) and the executive control network and reduced RS connectivity between the left angular gyrus and the anterior DMN during the luteal compared to the menstrual phase [46]. However, progesterone levels were unusually high during the menstrual phase, resulting in only a small difference in hormone concentration during the luteal phase. Additionally, no cycle-dependent estradiol differences were obtained; thus, the included subject might have been inaccurate in their cycle phase self-reports.

Hjelmervik et al. (2014) investigated four fronto-parietal (cognitive control) RS networks in a repeated measures design and could not find any cycle-related effect on RS connectivity [47]. These results are in line with those obtained by De Bondt et al. (2015). They also did not find any effect of sex hormones in fronto-parietal networks. However, in the DMN, an increase in RS connectivity between the network and the cuneus was observed in the luteal phase compared to the follicular phase [48].

Arélin et al. (2015) conducted 32 RS scans on a single subject across four menstrual cycles. Initial analyses revealed that high progesterone levels were associated with increased connectivity of the dorsolateral prefrontal cortex (dlPFC) and the sensorimotor cortex to the RS network. A region-of-interest analysis revealed that high progesterone levels were associated with higher RS connectivity between the right dlPFC, bilateral sensorimotor cortex, the hippocampus, and the left dlPFC and bilateral hippocampi during rest [49].

Finally, Weis 2019 et al. investigated sex hormonal effects on RS connectivity in the DMN and described variations in RS connectivity across the menstrual cycle [43].

Studying women during different cycle phases, as the menstrual cycle serves the most dramatic hormonal changes within short periods, has become a significant tool to investigate the influence

of sex hormones on cognitive behavior and its underlying functional brain organization.

This is from potential interest, as different menstrual cycle phases also affect cognitive function and psychological well-being.

Previous behavioral and neuroimaging studies have particularly shown the effects of the menstrual cycle on cognitive functions, for example, visuospatial ability [36], verbal skills [50, 51], and emotional memory [52]. Focusing on psychological well-being, a recently published meta-analysis summarizes that the menstrual phase during the menstrual cycle is associated with a greater risk of serious mental health outcomes, e. g., suicide attempts, psychiatric admissions, and drug abuse [53].

Thus, understanding the underlying principles of the mode of action of sex hormones in the brain is of high interest in the scientific community.

The role of 'the pill'

To make it even more complex, women experience dramatic hormonal changes during their lifetimes. With the advent of puberty, sex hormone levels increase immensely, with mean values being comparatively high for the following more than 30 years, known as reproductive years [54] before they relatively abruptly decline during the transition to reproductive senescence, commonly known as menopause [55].

However, women do not exclusively experience substantial alterations of sex hormones during their lifetime, but, with a focus on the reproductive years, in an approximately monthly manner, known as the menstrual cycle, but also due to the intake of OCs. Worldwide, more than 100 million people use hormonal contraceptives in the form of oral contraceptives (OCs) as a method of choice for contraception [56]; in Germany, it is more than half of the female population in their childbearing years between 18 and 49 years [57]. Comparable to the number of existing neuroimaging studies investigating the influence of naturally occurring sex hormones on brain functions is already limited, the number of studies examining the effect of synthetic hormones, particularly 'the pill', on the brain is also low. Surprisingly little is known about how the OCs affect the brain function of the user. For a decade, OCs were acknowledged to show an altered mate preference compared to non-OCs users [58] and different brain activation patterns while watching erotic stimuli [59]. Whereas these studies shed the first light on this topic, they are, of course, also entertaining and not only interesting to professional scientists. However, systematical investigations of OCs dependent changes in 'classical' robustly lateralized brain functions, e. g., language or visuospatial attention, using fMRI, are still rare. Rumberg and colleagues (2010) showed increased activation in right-hemispheric task-specific areas in OC users compared to non-users during a word generation task [51]. In addition, Pletzer and colleagues (2014) found more lateralized brain activation patterns in numerical tasks [38], in which cognitive demands can be related to spatial abilities [60]. Further brain function differences between OC users and non-users are described during resting state [46], and, for example, for reward- and face processing [61, 62].

The influence of the menstrual cycle and 'the pill' on brain structure

Brain structure differences between men and women have been described in several studies [63–65], with larger brains in males than in females, on average; for example, larger gray matter (GM) volumes in amygdalae, hippocampi, and temporal pole and orbitofrontal gyri in men, whereas women show larger thalami, precuneus, right insula cortex and right anterior cingulate gyrus [64]. Focusing on diffusion tensor imaging (DTI), studies comparing male and female brain anatomy are still rare. Menzler et al. (2010) described regional microstructural differences between male and female brains within the thalamus, corpus callosum, and cingulum. They concluded that higher values of fractional anisotropy and lower radial diffusivity in these areas were caused by differences in myelination between men and women [66]. These results are in line with the results of Dunst et al. (2014), who also described differences between male and female brains with regard to myelination [67].

Still, it's challenging to compare male and female brains, as the potential influence of sex hormones is hard to detangle. Women experience strong hormonal changes in sex hormones over their lifespan, whereas these levels are relatively constant in men. Therefore, investigating the cyclic fluctuation of female sex hormones during the menstrual cycle is a suitable tool to study these effects within a short period.

The fluctuation of female sex hormones during the menstrual cycle does affect not only brain function but also brain structure. The first results on this topic were reported over ten years ago by Protopopescu et al. (2008), who compared women in their late follicular phase (high estradiol, low progesterone) and mid-luteal phase (medium estradiol, high progesterone). They found increased gray matter (GM) volumes in the right anterior hippocampus and decreased values in the right globus pallidus and putamen in the late follicular phase [68]. These results were confirmed by Lisofsky and colleagues (2015) and, additionally, in a longitudinal single subject study [69, 70].

Partly supporting results were described by Pletzer et al. (2010), who described slightly larger GM volumes in the right parahippocampal/fusiform gyrus during their early follicular phase (low estradiol and progesterone) compared to their midluteal phase (medium estradiol and high progesterone levels) [71]. Further described brain regions, which are affected by different menstrual cycle phases, are the right middle frontal gyrus (MFG), the right anterior cingulate cortex (ACC), and the left insula. These regions showed larger volumes during the pre-ovulatory phase compared to the midluteal phase [72, 73]. Increased volumes in the left MFG but opposite results for the ACC were reported by Protopopescu et al. (2008) [68]. In a recent study on a sample of 55 women to assess menstrual cycle-dependent effects, there was a significant preovulatory estradiol-driven increase in bilateral hippocampal GM volumes and a significant progesterone-dependent increase in GM volumes of the right basal ganglia in the mid-luteal phase [74]. Further information concerning overall structural changes across different hormonal states within a woman's life, including brain maturation, puberty, menstrual cycle, OC intake, pregnancy, and menopause, is available within a recently published systemic review by Rehbein and colleagues (2020) [3].

Summarizing the above-described results, the hippocampus, basal ganglia, and insula are possible targets of structural changes due to sex hormones fluctuations during the menstrual cycle, accompanied by trend findings in parahippocampal and fusiform regions, the ACC and MFG.

The research field on the influence of the pill on brain structure is even younger. Around 10 years ago, Pletzer et al. (2010) published the first exploratory study [71]. They reported larger GM volumes in the prefrontal cortex, ACC, parahippocampal and fusiform gyri, and cerebellum in women using OCs. However, neither the 'pill's generation' nor the chemical combination of the OC was considered. That these issues hold a strong influence regarding brain structure, particularly GM volumes, could already be confirmed in a follow-up study conducted by the same authors a few years later. Pletzer and colleagues (2015) investigated the consequences of the use of so-called androgenic and anti-androgenic OCs, referring to their receptor binding properties and thus their ability to stimulate male characteristics [75], resulting in opposed effects on brain structure [76]. Whereas anti-androgenic OCs lead to larger gray matter volumes compared to women with a natural cycle, users of androgenic OCs displayed partly smaller brain regions in specific brain areas. In particular, whereas antiandrogenic OCs lead to larger GM volumes compared to women with a natural cycle in bilateral fusiform gyri, the fusiform face area (FFA), parahippocampal place area (PPA) and the cerebellum, users of androgenic OCs displayed significantly smaller brain regions in the bilateral middle and superior frontal gyri.

However, the authors did not control the exact hormone derivatives in the combined preparations. In general, the concentration of progesterone and estradiol derivates has been gradually reduced over the last decades to reduce side-effects [77]. However, different types of combinations may also still be associated with different side effects [78]. Whereas some progesterone derivates are considered to have androgenic properties, others, such as drospirenone and desorgestrel, may show anti-androgenic effects on the brain [79, 80]. The latter ones have also been postulated to be favorable regarding mood symptoms [81]. Besides the oral intake of hormonal contraceptives, alternative administration routes have been developed. Thus, hormones can be administered vaginally or transdermal. Additionally, long-acting-reversible contraception such as injections, implantable devices, and progesterone releasing intrauterine devices are effective contraceptive options [82]. However, the effect of these hormone administration pathways on the brain has not been extensively studied. This includes levonorgestrel-intrauterine-devices, although they are one of the most used contraceptive methods worldwide. Our findings align with a recently published study by Bürger et al. (2021) [83], who could not find these studies either. The lack of MRI studies investigating the effect of intrauterine devices on the brain might be their incompatibility with MRI scanners. There is a risk that the IUD may slip, reducing its contraceptive effect.

Gender identity and brain structure

A recently published study showed that even the identification of a gender role affected grey matter volume [84]. The author corroborated findings of sex hormones on brain structure and demonstrated testosterone-driven effects in women to more male-like brain morphologies. Furthermore, estradiol led to more female-like brain morphologies. The author described a positive association between a more feminine gender role and a more female-like brain morphology in men, notably concerning the left middle frontal gyrus. Additionally, differences in gender roles and gray matter volumes between OC-users and NC women were described [84]. Interestingly, focusing on the left middle frontal gyrus, this brain region is typically larger in women and has already been addressed in an earlier study where researchers reported larger cortical thickness in untreated male-to-female transsexuals compared to men [85]. These results are in line with prior results. A prior study showed that androgen treatment increases the female brain's volume towards male proportions, and anti-androgen and estrogen treatment reduced the size of the male brain towards a female morphology [86]. The findings imply the plasticity of the adult human brain structure towards the opposite sex under the influence of cross-sex hormones [86, 87].

Effects of gender-affirming hormone therapy (GHAT) on brain structure and function

Focusing on gender-affirming hormone therapy (GAHT) in transgender individuals to obtain their desired gender phenotype, longitudinal studies show that this therapy either feminizes brain structure in Male-to-Females (MTFs) or defeminizes brain structure in Female-to-Males (for a review please see [88]). Particularly, in MTFs, a duration of four months of anti-androgen and estrogen GAHT resulted in decreased brain volumes in the right hippocampal region and increased ventricle volumes compared with male controls [89]. Additionally, the decrease in brain volume was correlated with changes in progesterone levels. Another study reported an increase in total brain and hypothalamic volume and decreased ventricle volumes compared with female controls [90]. However, these studies display plastic changes in specifically subcortical structures related to memory and emotional processing [88].

Regarding brain function, Sommer et al. [91] detected a potential influence of three months of GAHT on brain activation patterns during language and mental rotation tasks in eight MTFs and six FTMs individuals with lateralization of both evoked activations remaining stable. Additionally, they reported a correlation between the total increase of language-related activation after GAHT with post-treatment serum estradiol levels and post-treatment testosterone levels with full brain activation during mental rotation. In summary, the application of MRI to the investigation of the transgender brain and the effects of GAHT is still in its infancy, and data is yet only derived from small sample sizes; however, it offers an excellent tool to understand regional and network effects of hormonal treatments on the brain.

What is the challenge of investigating the effect of sex hormones on the brain?

Despite the early research interest in this topic in general over 80 years ago [92], it is highly surprising that only a handful of scientists worldwide are actively examining the effect of sex hormones on the brain, no matter if they occur physiologically during a woman's lifespan (e. g., puberty, pregnancy, menopause), or how the application of hormonal contraceptives influence and manipulate

their effects. One should think that nowadays, elaborated neuroimaging methods are feasibly available and could easily shed light on this intriguing topic, affecting millions of women worldwide. Thus, it might sound surprising at first glance; however, scientists have been aware of methodological issues and challenges since the early 70 s. Here, Sommer (1973) reviewed 33 publications investigating the effect of the menstrual cycle on cognition and perceptual motor behavior and found no evidence. However, she concluded that this result might be due to methodological problems, which researchers are confronted by when investigating the menstrual cycle [93]. This issue might be an explanation for the relatively small amount of neuroimaging studies. Additionally, these studies, which are reviewed to a significant part by Sundström Poromaa & Gingnell (2014), are not consistent concerning the obtained results and the described hormonal effects [94]. Not only is it very time consuming, but also the exact determination of hormonal state, e. g., from collected blood or salvia samples, has often not been state of the art yet. For example, in Protopopescu and colleagues' study (2008), the menstrual cycle phase definition was very lenient, as it did not include hormone analyses [68]. Pletzer and colleagues also relied on verbal reports in one of their studies [38], and so did Rumberg et al. 2009 [51].

Furthermore, infrastructural issues occur; for example, MRI measurement appointments need to be reserved and are often not spontaneously available; blood- or salvia samples need to be pretreated and correctly stored. These additional barriers and challenges might also explain the usually meager number of initially investigated subjects (e. g., [71] only included 14 subjects) and the high drop-out numbers caused by later correction of the cycle phases.

Concerning the studies investigating the effects of OC, a further difficulty occurs: OCs are available in various combinations of synthetic hormones, particularly with regard to their androgenic modes of actions. These issues hold a strong influence regarding brain structure, as has been confirmed for instance in a follow-up study by Pletzer and colleagues (2015). As written above, they examined the effects of androgenic and antiandrogenic OCs, resulting in opposed impacts on brain structure. However, again, they did not control for the exact hormone derivatives in the combined preparations [95].

These methodological challenges have already been clearly recognized several years ago. Pletzer and Kerschbaum (2014), for instance, stated almost ten years ago that more systemic research is needed to *"reveal the true nature of OC-dependent effects on cognition as well as the impact of synthetic steroids on neuronal correlates"* [79]. Accordingly, previous study results must be considered with reservations, as different cycle phases were compared, relatively small sample sizes were examined, and exact hormonal determination is not present in all studies. Past studies relied on self-reports, which were rather unspecific and accompanied by high drop-out rates. Other studies did not determine hormonal concentrations at all; consequently, data collection on the requested cycle phase cannot be guaranteed. Focusing on the effect of OCs on brain structure, former studies did neither control for 'the pill generation' nor the exact chemical combination. Additionally, different analysis pipelines were applied, using different brain parcellations, thus impeding the comparability of the yielded results.

With regard on brain function, fMRI studies, the method itself is challenging. With a boost of awareness regarding a concerning shortage of reliability and reproducibility in neuroscientific research, the degree of validity of the yielded results has become uncertain. Various forms of instability have been identified in structural and functional measurements, including across operating system versions [96], minor noise injections ([97], and data set or implementation of theoretically equivalent algorithms [98, 99]. These issues hold practical applications in order to decide which tool/implementation should be applied for an experiment [100]. Focusing on conventional fMRI, regional brain activity is estimated by measuring the BOLD signal that indicates changes in blood oxygenation associated neural activity [101]. Commonly, researchers map brain activity evoked by specific cognitive functions by contrasting the regional BOLD signal during a control condition with the BOLD signal during a condition of interest [102]. Thanks to this approach, task-fMRI enables unique insights into the brain, ranging from basic perception to complex thought and, with a clinical focus, the opportunity to directly measure neurological and psychiatric dysfunction [102]. The original idea of task-fMRI was to examine functions of the average human brain by measuring within-subject differences in brain activation between task and control conditions and averaging them together across subjects to obtain a group effect, resulting in mostly robust brain activity. This led to the idea of using the same paradigms to study between-subject differences. Thus nowadays, fMRI is widely used for studying how the brains of individuals differ. However, the reliability of the most commonly applied paradigm is largely unknown and an object of current debate within this research field [103–105]. Recently, concerns have been raised that the conclusions drawn from some neuroimaging studies are either bogus or not generalizable. This might be caused by the high vulnerability of fMRI results to low statistical power, flexibility in data analysis, software error, and a lack of direct replication [106].

Focusing on visuospatial attention, by now, available paradigms investigating visuospatial functions provide widely distributed activation patterns and markedly inter- as well as intra-subject heterogeneity; thus they would add further variability and might reduce the obtained effect sizes [107].

Behavioral studies show that spatial tasks favor men and that women during high-hormonal phases, notably late follicular- and luteal phase, score lower on mental rotation tasks than during the low-hormonal phase [108]. Surprisingly, the effect of OCs and particularly their androgenic activity has not been systematically investigated using fMRI, despite a behavioral study impressively demonstrated that performance in the applied mental rotation task was best in OC users on an androgenic treatment compared to users of antiandrogenic OCs and nonusers [109].

Necessary prerequisites to study the influence of sex hormone on the brain using MRI

These limitations, however, highlight that future refinement of the utilized paradigms is strongly needed and is an essential prerequisite for a more thorough investigation of the right-hemispheric lateralization in visuospatial attention. This is even more important before applying these paradigms, providing rather heterogeneous activation patterns across subjects to research questions, which

expect to obtain comparatively small differences. This is the case when studying the effects of sex hormones on the brain. Regarding data collection and analysis, it is thus recommended to include robust and reliable fMRI paradigms to increase the obtained data's validity.

Future studies are advised to consider the following recommendation concerning the study design: Investigating women with a menstrual cycle, favorably several cycle phases is favorable and depends on the research focus. Concerning this point, different questions concerning the effects of menstrual cycle phases and OC intake need to consider distinct cycle phases: Whereas studying the potential effects of sex hormones on different brain functions, particularly their degree of lateralization, might be most suitable for comparing high- and low progesterone driven cycle phases (with regard to the progesterone dependent hemispheric decoupling hypothesis [12]; structural differences might be more prominent during high- and low estradiol differing phases [68, 69, 71–73].

Still, it is not possible to narrow down the obtained results to either estradiol or progesterone as both hormones are constantly present in the organism and interact with each other. The endogenous release of progesterone during the luteal phase is always accompanied by release of estradiol. The release of other hormones could also alter the responsiveness of progesterone or estradiol in the brain [110, 111]. However, the use of sophisticated statistical analyses, for example linear mixed effects models, has made it possible to identify hormonal key players within a specific cycle phase. This procedure is well described in Pletzer et al. 2018 [74]. Additionally, it is important to validate cycle phases by evaluating the exact hormone concentration in, e. g., blood samples. When investigating women under an OC-treatment, it is highly recommended to include only one explicit OC-type per test group, containing the exact amount of estradiol and progestin derivatives. For all women, a sophisticated anamnestic interview is advised, including each individual's hormonal history, e. g., previous pregnancies, use of other oral contraceptive types, or hormonal replacement therapies, as these have shown an impact on the human brain [112, 113].

Furthermore, scientists have to be careful with regard to the results' interpretation. As menstrual cycle phases are governed largely by the concentration and fluctuation of the captured female sex hormones estradiol and progesterone, these might not be the only potential important influence factors affecting GM volumes. As already described earlier, the natural menstrual cycle as well as OCs affect various metabolic processes (e. g., basal body temperature, heart rate, and breathing patterns), which might affect the measured MRI signal.

Additionally, a recently published study described that menstrual cycle affects cerebral blood flow CBF as well, which is in turn crucial for functional MRI, determined by changes in the BOLD signal [114]. It is already known that estradiol has excitatory and vasodilatory effects in arteries, which could lead to widespread increases in CBF. In contrast, progesterone may have opposing effects on CBF. As estradiol and progesterone receptor density vary across the cortex [115], thus effects may be stronger in specific brain areas. To elucidate the potential effects of hormones on blood flow on the brain, Cote et al. directly investigated the link between CBF and estradiol and progesterone, while controlling for the size of the large feeding arteries using a multi-modal approach combining arterial spin labeling (ASL) and non-contrast-enhanced Time-Of-Flight (TOF) magnetic resonance angiography [114]. They observed a relatively strong, inverse relationship between progesterone levels during the luteal phase and CBF during the same phase, with the strongest link in frontal cortex. Serum estradiol during the follicular phase tended to correlate weakly with CBF during this cycle phase. Additionally, during the luteal phase, estradiol did not impact the relationship between progesterone and CBF, nor did the lumen diameters of the large arteries feeding the anterior and posterior circulation. They concluded that estradiol and progesterone have strikingly different and independent effects on CBF, which are unlikely to be driven by large artery morphology. Furthermore, they showed that CBF is dynamic and related to the hormonal state in women. These results are crucial with regard to fMRI studies, as these results are obtained from the BOLD signal, which in turn is affected by the CBF.

Therefore, the results cannot be interpreted solely as a direct effect of fluctuating sex hormones on the brain but could also be evoked by further physiological parameter changes. Additionally, the decision to start or end treatment of OCs might also be accompanied by changes in personal circumstances that, in turn, may affect overall psychological well-being.

Thus, it is practically impossible to detangle and identify the sole effect of the hormonal key players of the menstrual cycle on the female human brain.

Additionally, fMRI paradigms that assess emotion and empathy processing, as well as social interactions, should be included to investigate sex hormones' effects on these essential interpersonal functions. Including various neuropsychological tests and questionnaires could further increase knowledge about the hormonal effects on cognition and psychological well-being.

An elucidation of how hormones affect our brain will also help us to better understand disorders such as premenstrual syndrome, and postnatal depression and ultimately to be able to treat them successfully. This may also help us to understand what might have motivated ancient Greek anatomists to name the uterus after a former psychiatric illness.

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Conflict of Interest

The authors declare that they have no conflict of interest

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