WOMEN'S HEALTH

The monthly rhythm of the brain-heart connection

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Integrating the menstrual cycle into heart-brain research is a crucial step toward advancing sex-specific medicine and improving outcomes for female brain and body health.

Cognitive neuroscience and neurology seek to understand the complexities of the human brain across the lifespan. Recent research highlighting how bodily rhythms, including the cardiac cycle, modulate brain activity, cognition, and behavior has led to an increasing emphasis on an integrated understanding of the brain-body connection. The interplay between the heart and the brain—mediated through neural, hormonal, and autonomic pathways (Fig. 1, top)—is increasingly recognized as central to understanding cardiovascular risk and neurovascular conditions. Both organs are profoundly affected by the neuroendocrine system and hence significantly shaped by sex (and gender). The menstrual cycle, influencing the daily physiological and cognitive experiences for more than 1.8 billion individuals menstruating every month, emerges as a key opportunity to noninvasively study hormone-driven plasticity in cardiac physiology and brain-heart interactions.

Fluctuations in endogenous ovarian hormones across the menstrual cycle, such as estrogen and progesterone, directly and indirectly modulate various components of the heart-brain axis. Cardiomyocytes have receptors for both hormones, allowing them to directly influence electrophysiological properties and cardiac function (bottom arrows, Fig. 1, top) (*1*). In addition, animal research on ovarian hormones revealed high densities of estrogen and progesterone receptors in brain regions important for autonomic control (*2*) (see Fig. 1, top), which is paralleled by profound variation in heart rate and heart rate variability throughout the human menstrual cycle. The heart rate increases by an average of 2.33 beats per minute during the luteal phase, when endogenous progesterone levels peak, compared to the follicular phase, when estrogen and progesterone concentrations are low, with this increase linked to reduced parasympathetic (vagal) control over the heart (*3*) (Fig. 1, bottom). For completeness, cyclic variations in circulating ovarian hormones also strongly influence uterine autonomic innervation (Fig. 1, top), with sympathetic nerves in the uterus being most susceptible to degeneration when estrogen levels are high [for an extensive overview, see (*4*)].

A relevant neuromolecular mechanism for heart-brain adaptability over the menstrual cycle may be found in the regulation of γ-aminobutyric acid type A ($GABA_A$) receptors, the central nervous system's primary inhibitory receptor, by neurosteroid synthesis. Careful mechanistic work has revealed that allopregnanolone, a neuroactive metabolite of progesterone, acts as a positive allostatic modulator of the $GABA_A$ receptor that enhances the tonic inhibition mediated by these receptors, with profound implications for mood (*5*). The medial prefrontal cortex, particularly rich in $GABA_A$ receptors, plays a crucial region in maintaining cardiac autonomic control by exerting a continuous inhibition over the sinoatrial node (the heart's "pacemaker") and promoting cardiac vagal tone. Cyclical surges in allopregnanolone, which enhance GABA's inhibitory effects, may hypothetically suppress this prefrontal top-down control, contributing to the observed increases in heart rate during the progesterone-dominated luteal phase.

In contrast, estradiol's cardioprotective effects are well studied in animal models (*1*), revealing that estradiol enhances choline uptake and acetylcholine synthesis—the primary vagal neurotransmitter—which promotes parasympathetic tone and lowers heart rate. However, human studies assessing heart rate during the ovulatory phase of the menstrual cycle, when estradiol levels peak, are currently limited (*3*).

PERCEIVING THE HEART'S INTERNAL STATE

The (patho)psychological consequences of these hormonal fluctuations on cardiac autonomic regulation remain to be fully understood. Given the connection between heart rate variability and self-regulatory abilities (*6*), it is likely that hormonal shifts during the menstrual cycle have a significant impact on stress reactivity and affective regulation. These hormonal variations may also influence associated cognitive processes—such as cardiac interoception, i.e., our ability to perceive the heart's internal state—which are crucial for emotional processing and homeostatic regulation. Poor cardiac interoception is increasingly linked to mental health vulnerabilities, such as anxiety and depression, which disproportionally affect females. Although females report heightened attention to their bodily signals, they consistently underperform on cardiac interoception tests compared to men according to a recent meta-analysis (*7*). While sex hormones likely play a role in this disparity, systematic investigations into hormonal status have been limited.

From a clinical point of view, both the heart and brain share common vulnerabilities, with risk factors such as hypertension, diabetes, smoking, or dyslipidemia simultaneously affecting heart and brain health. Although the

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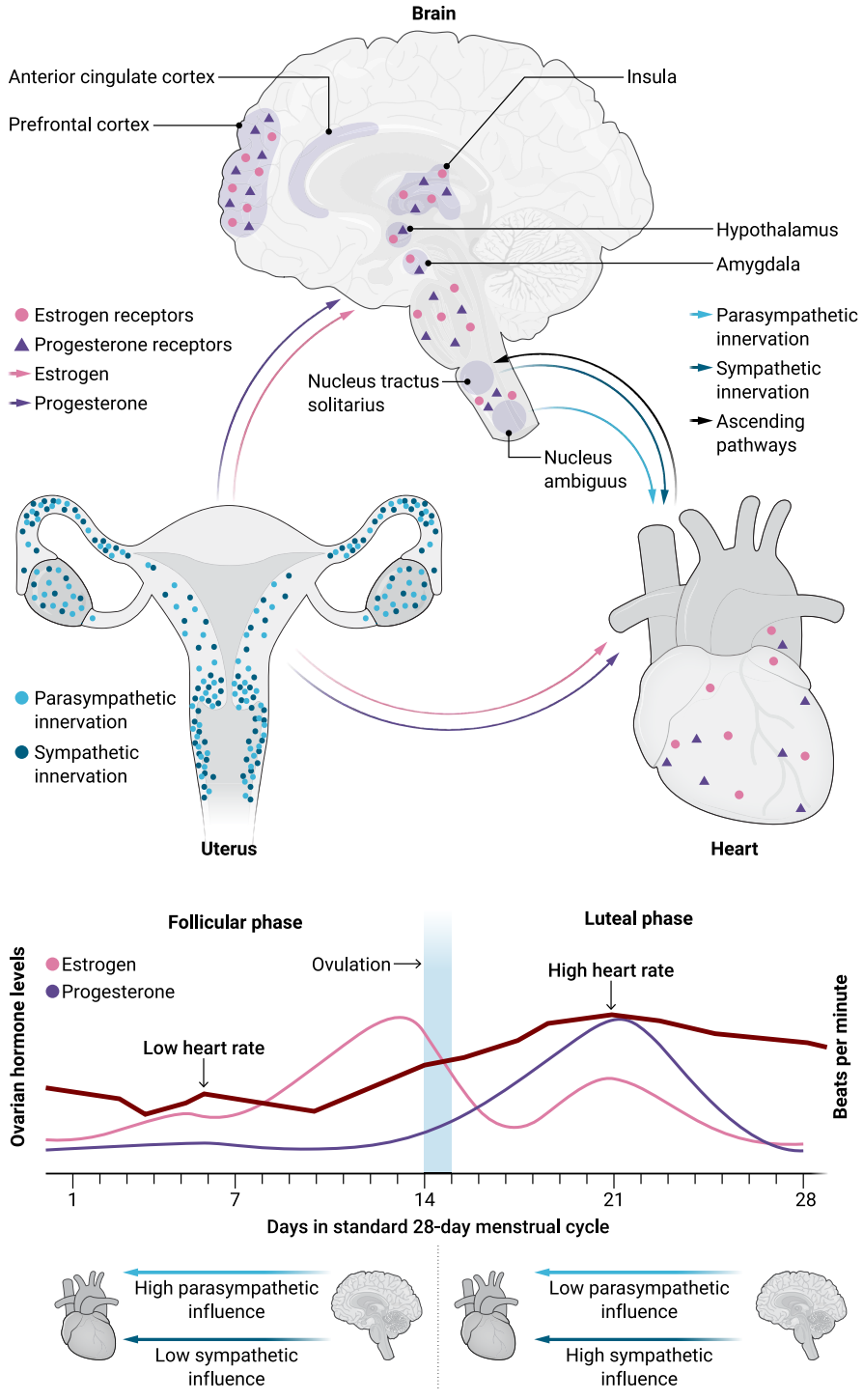

Fig. 1. Role of endogenous ovarian hormone fluctuations on the heart-brain axis during the menstrual cycle. (**Top**) Expression of estrogen and progesterone receptors in brain regions important for cardiac autonomic control, as well as the interplay between sympathetic and parasympathetic innervation in the uterus and heart. Hormonally mediated adaptability along the heart-brain(-uterine) axis is a highly complex phenomenon, driven by multiple neurobiological, neurochemical, and neurophysiological mechanisms. Multiple critical knowledge gaps persist in this area. (**Bottom**) Fluctuations in the female resting heart rate across the menstrual cycle. On average, resting heart rate increased by 2.33 beats per minute during the midluteal phase when progesterone levels are high. The underlying neuromolecular mechanism as well as the (patho)psychological implications of these hormonal fluctuations on the heart-brain connection and associated cognitive functions remains to be fully understood. Illustration credit: A. Mastin/*Science Advances*

historical male bias in clinical research, with findings being applied to clinical care in a sex-agnostic manner, has left critical gaps in understanding female cardiac (patho)physiology and the role of endocrine factors, cardiology has been at the forefront of sex-specific medicine (*8*). This progress is evident in several key findings. For example, sex differences in autonomic function are known to translate to differential responses to β-adrenergic blocking agents (β-blockers) between males and females (*9*). Arrhythmias are more frequent in women than men and show increased prevalence during the luteal phase (*10*).

Despite these advances in cardiology, psychiatry and clinical neuroscience have yet to fully embrace the importance of endocrine factors in understanding the brain-heart connection. Progress in this area will be crucial for unlocking new strategies to improve both mental and heart health in women, ultimately advancing female hormone–informed clinical care. For instance, a deeper understanding of how menstrual cycle phases influence the brain-heart axis may help identify vulnerable time windows for females with cardiac arrhythmias, hypertension, or anxiety disorders. The menstrual cycle phase could become an important variable in the screening and diagnosis for arrhythmias and cardiovascular events that show increased prevalence in the luteal cycle phase (*10*). In addition, since the luteal phase is associated with reduced cardiac vagal tone (*3*), females with particular cardiac risk might benefit from closer monitoring or tailored lifestyle modifications during this phase.

Different components of the heart-brain axis can be targeted to induce changes in the system. Propranolol, a β-blocker with both central and peripheral mechanisms of action, was originally developed for treating cardiovascular conditions but is now actively explored as a treatment for anxiety disorders. Research shows that propranolol effectively ameliorates emotional and physical symptoms in the luteal phase in females with severe premenstrual symptoms (*11*). Further exploring cardiac medications as adjunctive treatments for luteal autonomic stress, premenstrual anxiety, or irritability could open promising new therapeutic avenues. Conversely, the successful example of synthetic allopregnanolone administration in (reproductive) mood disorders highlights the translational potential of hormonal mechanisms for therapeutic innovation in psychiatry (*5*). Similarly, the cardioprotective effects of estradiol, demonstrated in animal models (*1*), warrant further

exploration for their potential to mitigate brain and cardiac dysregulation, such as in anxiety disorders.

Last, sex hormones can influence the pharmacodynamics and efficacy of various medications (*9*), suggesting the need for dose adjustments tailored to the menstrual cycle phase. For instance, increased β-blocker dosage may be more effective during the luteal phase when cardiac parasympathetic activity decreases, whereas reduced doses could suffice during the follicular phase.

OPPORTUNITIES FOR RESEARCH

When studying the brain-heart axis, a field in which clinical sex differences are commonly observed, it is critical to account for ovarian hormone–induced variability. The menstrual cycle offers a unique, noninvasive opportunity to investigate how subtle yet systemic fluctuations in endogenous sex hormones affect the brain-heart connection. However, rarely has systematic menstrual cycle monitoring been used, contributing to inconsistencies in the literature. To facilitate more rapid accumulation of knowledge on cycle effects, a set of integrative guidelines and standardized phasing procedures was recently introduced (*12*). Three main steps to increase precision in menstrual cycle tracking include the following: (i) addition of tracking to subject designs and repeated measures—it increases sensitivity to hormonal effects and reduces variability in findings; (ii) precise and reliable hormonal measurement—use of gold-standard methods, such as liquid chromatography–mass spectrometry, ensures robust determination of ovarian hormones (e.g., estradiol, progesterone, and luteinizing hormone) and menstrual cycle phase; and (iii) tracking menstrual cycle regularity—combining digital apps or journals with hormonal assays enables accurate alignment of experimental measures with specific cycle phases.

The menstrual cycle presents a powerful lens through which to explore the dynamic and systemic effects of sex hormones on the brain and heart. Robust research can result from investigating hormone-driven plasticity and its implications for cognitive, emotional, and autonomic regulation. Identifying changes linked to the menstrual cycle during reproductive years could guide future research on how more pronounced hormonal transitions—such as puberty, pregnancy, menopause, hormonal contraception, or gender-affirming hormone therapy—affect the brain-heart axis. By exploring how hormonal states influence the central autonomic network and peripheral cardiac responses, future research could facilitate early detection of conditions like anxiety and cardiovascular disease by identifying windows of heightened risk during the menstrual cycle. This work can inform phase-specific interventions, such as tailoring treatments for mood disorders or autonomic dysfunctions to specific hormonal states. Such research can also support hormone-informed personalized medicine approaches by integrating hormone profiles into treatment plans for disorders influenced by brain-heart dynamics. Addressing these research gaps is essential for advancing mental and cardiovascular health for all.

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