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Whole-brain dynamics across the menstrual cycle: the role of hormonal fluctuations and age in healthy women

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Recent neuroimaging research suggests that female sex hormone fluctuations modulate brain activity. Nevertheless, how brain network dynamics change across the female menstrual cycle remains largely unknown. Here, we investigated the dynamical complexity underlying three menstrual cycle phases (i.e., early follicular, pre-ovulatory, and mid-luteal) in 60 healthy naturally-cycling women scanned using resting-state fMRI. Our results revealed that the pre-ovulatory phase exhibited the highest dynamical complexity (variability over time) across the whole-brain functional network compared to the early follicular and mid-luteal phases, while the early follicular showed the lowest. Furthermore, we found that large-scale resting-state networks reconfigure along menstrual cycle phases. Multilevel mixed-effects models revealed age-related changes in the whole-brain, control, and dorsal attention networks, while estradiol and progesterone influenced the whole-brain, DMN, limbic, dorsal attention, somatomotor, and subcortical networks. Overall, these findings evidence that age and ovarian hormones modulate brain network dynamics along the menstrual cycle.

Approximately 49.7% of the world's female population are women of reproductive age (15–45 years old). Of these women, around 58% experience a natural menstrual cycle (free of hormonal contraceptives), characterized by physiological fluctuations of the ovarian hormones estradiol and progesterone[1–4]. A regular menstrual cycle ranges between 21 to 35 days with less than seven days of variability in cycle length[5] and can be divided into three main phases according to the hormonal levels. The onset of menses initiates the follicular phase and marks the beginning of the menstrual cycle. The follicular phase is characterized by low progesterone levels and a gradual increase in estradiol concentrations until the pre-ovulatory phase, in which estradiol levels reach their peak. Following ovulation, the luteal phase commences and continues until the last day of the menstrual cycle. This phase is characterized by an increase in progesterone levels, which reach their highest peak in the middle of the phase[6,7]. Converging and growing evidence shows that these cyclic hormonal fluctuations impact brain structure and function in multiple ways[1,8–15]. Especially, large-scale network dynamics have proven responsive to endogenous hormonal fluctuations[11,16].

Resting-state fMRI enables exploring the brain's intrinsic organization of large-scale distributed networks. Recent neuroimaging studies on the menstrual cycle have revealed cycle-related brain activity fluctuations in several resting-state networks, including the default mode network (DMN), salience, dorsal attention, and subcortical networks[11,17–21]. For instance, studies have shown that the connectivity of the DMN changes throughout the menstrual cycle[21]. Increased connectivity between the DMN and the left middle frontal gyrus was found in the early follicular phase compared to the mid-follicular phase. By contrast, decreased connectivity between the DMN and the left angular gyrus was observed in the luteal phase compared to the early follicular phase[18,20]. Dynamic changes across the cycle phases have been shown to involve a reorganization of salience and executive control networks depending on the hormonal levels[22].

However, prior menstrual cycle research has focused on studying specific brain regions using static approaches. Thus, a comprehensive understanding of the impact of hormonal fluctuations on whole-brain dynamics is lacking. To date, only a few menstrual cycle fMRI studies have

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used a whole-brain dynamic approach and showed that progesterone and estradiol impact brain dynamics and information processing across large-scale brain networks[11,12,23,24]. Specifically, high estradiol levels have been shown to modulate the DMN and the dorsal attention network[11]. During the ovulatory phase, brain dynamics exhibit increased flexibility among prefrontal, limbic, and subcortical nodes compared to the follicular and luteal phases[12]. Furthermore, the luteal phase shows higher information transmission across spatial scales compared to the follicular phase[23]. In addition, recurring network states of high-amplitude dynamic functional connectivity have been linked to fluctuations in follicle-stimulating and luteinizing hormones[24]. However, these studies were based on a dense-sample dataset (N=1) of a woman in her twenties, presenting some limitations. Notably, variations in brain activity patterns among women may arise due to diverse factors, including age, hormone sensitivity, or expression of sex hormone receptors[8]. Addressing these limitations is critical for providing a more reliable understanding of how menstrual cycle-related changes impact cognition, emotion, and behavior, as well as for developing targeted interventions for menstrual cycle-related disorders. Thus, further investigations are needed to enhance our understanding of the complex interplay between sex ovarian hormones and brain dynamics.

The dynamic intrinsic ignition framework provides a comprehensive view of the brain as a complex system that exhibits specific dynamical properties essential for effective information processing[25,26]. This framework emphasizes the concept of intrinsic ignition, which refers to the ability of brain areas to transmit unidirectional and recurrent neural activity to other areas across the whole brain network, and is related to the levels of metastability[26]. Metastability in a brain area (i.e., node-metastability) is a measure of diversity across time, which is linked to the fundamental functionality of a given area. Different levels of temporal diversity in a given brain area can be considered a measure of local functional variability or metastability and thus describe the versatility of a given brain area. At rest, the brain operates optimally in high metastable dynamical regimes, contributing to cognitive flexibility, whereas low metastability is related to a reduction in dynamical complexity and information processing[27,28]. This framework has proven remarkably robust in capturing subtle differences in whole-brain dynamics across several brain states in health and disease, including deep sleep, meditation, aging, depression, and abnormal development, among others[26,29–32]. The impact of menstrual cycle phases and hormone levels on the female brain can be determined by examining the underlying whole-brain dynamics, as it provides a comprehensive understanding of the processes governing brain function, the interaction of different brain areas and adaptive changes over time.

In this study, we aimed to investigate the dynamical complexity of the menstrual cycle phases by examining resting state activity at different levels of analysis, including global, network and local brain activity patterns in a sample of 60 healthy naturally-cycling women scanned using resting state fMRI. Specifically, we computed the intrinsic ignition framework[25] to measure brain dynamics across the whole-brain network and within eight well-known resting-state networks (control, DMN, dorsal attention, limbic, somatomotor, salience, subcortical, and visual) along three menstrual cycle phases (early follicular, pre-ovulatory, and mid-luteal). Furthermore, we employed multilevel modeling to examine the effects of hormone levels (progesterone and estradiol) and age on whole-brain and resting-state network dynamics. We hypothesized that hormone levels and age can substantially influence brain network dynamics.

Results

Demographic and hormonal data

This study analyzed a cohort of 60 young healthy women with a regular menstrual cycle as previously reported in Hidalgo-Lopez et al.[16]. The participants had an average age of 25.4 years (range 18–35 years), and their average cycle length was 28 days (range 23-38). Mixed effects models show that estradiol levels were significantly higher during the pre-ovulatory than the early follicular (*Estimate* = 0.329, *SE* = 0.051, FDR-corrected $p < 0.001$) or mid-luteal phase (*Estimate* = − 0.178, *SE* = 0.051, FDR-corrected $p = 0.003$) and higher in the mid-luteal than the early follicular phase (*Estimate* = 0.151, *SE* = 0.051, FDR-corrected $p = 0.009$). Progesterone levels during the mid-luteal phase were significantly higher than those during the pre-ovulatory phase (*Estimate* = 116.34, *SE* = 13.05, FDR-corrected $p < 0.001$) and early follicular phases (*Estimate* = 138.74, *SE* = 13.05, FDR-corrected $p < 0.001$). Hormonal results were as expected for healthy women in each phase of the menstrual cycle. See Table 1 and Fig. 1.

Node-metastability across the whole-brain network

For each menstrual cycle phase, we computed the node-metastability measure to study the dynamical complexity underlying the whole-brain functional network (Fig. 2 and Methods). We found that the dynamical complexity was higher in the pre-ovulatory phase compared to the early follicular ($p < 0.001$, Monte Carlo permutation and FDR-corrected) and mid-luteal ($p < 0.001$, Monte Carlo permutation and FDR-corrected) phases. Furthermore, we found that the dynamical complexity was higher in the mid-luteal phase than in the early follicular phase ($p < 0.001$, Monte Carlo permutation and FDR-corrected) (Fig. 3a). In Fig. 3b, we show the hierarchy for each phase across the whole-brain functional network (i.e., brain areas sorted from highest to lowest node-metastability). The red area represents the 10% brain areas showing the highest node-metastability values for each phase. For the early follicular phase, the brain areas showing the highest values of metastability were primarily located in the attentional networks, DMN, visual, and somatomotor. For the pre-ovulatory phase, brain areas with the highest metastability belonged to the DMN, limbic, subcortical, dorsal attention, and control networks. During the mid-luteal phase, the top brain areas were mainly located in the subcortical network, dorsal attention, and control networks. In Fig. 3c, we show the rendered brains representing the node-metastability for each phase across the whole-brain functional network. It is clear that the pre-ovulatory phase shows the highest metastability values compared to the early follicular and mid-luteal phases.

Node-metastability across resting state networks

We independently computed the node-metastability measure within each resting-state network. Differences among menstrual cycle phases for each network are presented in Fig. 4a. First, the pre-ovulatory phase showed significantly increased dynamical complexity compared to the early follicular phase in the DMN, visual, subcortical ($p < 0.001$, Monte Carlo permutation and FDR-corrected), limbic, control, salience ($p < 0.05$, Monte Carlo permutation and FDR-corrected); however, the control network did not survive multiple comparisons correction ($p = 0.067$). In contrast, the pre-ovulatory phase showed lower dynamical complexity compared to the early follicular phase in the dorsal attention network ($p < 0.05$, Monte Carlo permutation and FDR-corrected). Second, the mid-luteal phase showed significantly increased dynamical complexity compared to the early follicular phase in the DMN, subcortical ($p < 0.001$, Monte Carlo permutation

Table 1 | Hormonal and cycle days data for the 60 participants

	Estradiol (*pg/ml*)	Progesterone (*pg/ml*)	Cycle days
Early follicular	0.84 ± 0.46 (0.23–2.41)	68.77 ± 44.37 (7.89–177.97)	3.72 ± 1.51 (1–7)
Pre-ovulatory	1.17 ± 0.62 (0.23–4.02)	91.18 ± 67.34 (10.69–323.21)	12.08 ± 2.43 (5–21)
Mid-luteal	0.99 ± 0.45 (0.37–2.36)	207.52 ± 144.61 (48.47–625.59)	21.37 ± 3.57 (15–37)

We present the mean values, ±standard deviation, and range in parentheses.

and FDR-corrected), and limbic networks ($p < 0.05$, Monte Carlo permutation and FDR-corrected), but showed decreased dynamical complexity in the dorsal attention, salience, and somatomotor networks ($p < 0.001$, Monte Carlo permutation and FDR-corrected). Finally, compared to the pre-ovulatory phase, the mid-luteal phase showed significantly increased complexity only in the DMN ($p < 0.05$, Monte Carlo permutation and FDR-corrected) but lower dynamical complexity in the visual, salience, and somatomotor networks ($p < 0.001$, Monte Carlo permutation and FDR-corrected). Figure 4b shows a radar plot representing the average metastability values for each resting-state network in each menstrual cycle phase.

Mixed effects models of age and ovarian hormones on brain dynamics

Mixed effects models were carried out to investigate the effects of estradiol, progesterone, and age on brain dynamics. Node-metastability values

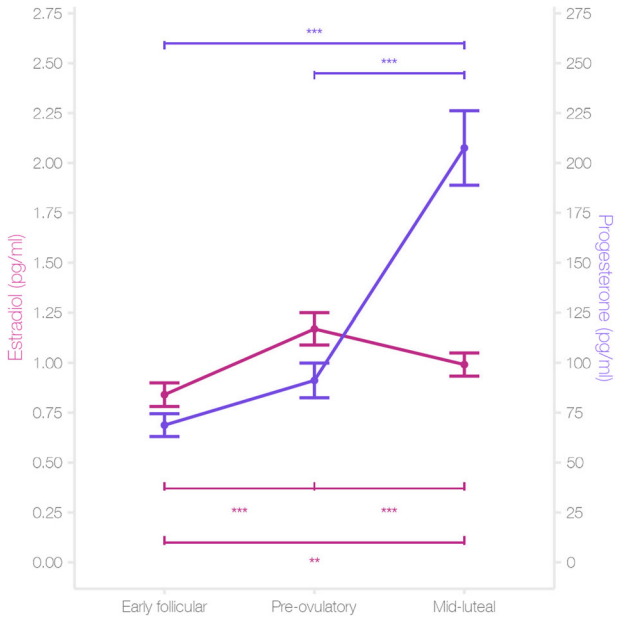

Fig. 1 | Estradiol (magenta) and progesterone (violet) levels during each menstrual cycle phase. Data is presented as mean ± SE and were analyzed by mixed effects models. Significant differences are denoted by ***$p < 0.001$, and **$p < 0.01$.

associated with each network for each woman were introduced as a dependent variable (see Statistical analyses section). Results are displayed in Fig. 5. For the whole brain, age (*Estimate* = 0.001, *SE* = 0.001, $p = 0.033$), estradiol (*Estimate* = 0.007, *SE* = 0.001, $p < 0.001$), progesterone (*Estimate* = 0.000, *SE* = 0.000, $p = 0.028$), and the interaction between both hormones (*Estimate* = − 0.000, *SE* = 0.000, $p = 0.006$) showed a significant effect. These results indicate higher levels of metastability in the whole-brain network with increased age, estradiol, and progesterone. Furthermore, the significant interaction between hormones shows that metastability increases in the whole brain when estradiol levels increase and progesterone levels decrease. For the DMN, estradiol (*Estimate* = − 0.005, *SE* = 0.002, $p = 0.022$) and progesterone (*Estimate* = 0.000, *SE* = 0.000, $p < 0.001$) showed a significant effect. This result indicates that higher estradiol levels predict lower metastability, while higher progesterone levels predict higher metastability. For the limbic network, estradiol (*Estimate* = 0.019, *SE* = 0.005, $p < 0.001$), progesterone (*Estimate* = 0.000, *SE* = 0.000, $p < 0.001$), and the interaction between both (*Estimate* = − 0.000, *SE* = 0.000, $p = 0.002$) show a significant effect. These results indicate that higher estradiol and progesterone levels predict higher metastability. In the control network, higher age levels predicted increased metastability (*Estimate* = 0.002, *SE* = 0.001, $p = 0.002$). For the dorsal attention network, age (*Estimate* = 0.002, *SE* = 0.001, $p = 0.011$), estradiol (*Estimate* = 0.008, *SE* = 0.004, $p = 0.021$), progesterone (*Estimate* = 0.000, *SE* = 0.000, $p < 0.001$) and interaction between hormones (*Estimate* = − 0.000, *SE* = 0.000, $p = 0.000$) revealed a significant effect. These results indicate that higher age predicted increased metastability. Additionally, the significant interaction between hormones shows that metastability decreases when estradiol levels decrease and progesterone levels increase. In the salience network, a significant effect was observed for the hormone interaction (*Estimate* = − 0.000, *SE* = 0.000, $p = 0.040$), indicating increased metastability with elevated estradiol levels and decreased progesterone levels. The somatomotor network, estradiol (*Estimate* = − 0.010, *SE* = 0.004, $p = 0.011$), progesterone (*Estimate* = − 0.000, *SE* = 0.000, $p < 0.001$) and the interaction between both (*Estimate* = 0.000, *SE* = 0.000, $p < 0.001$). The results indicate that this network exhibits lower metastability when progesterone levels increase, and estradiol levels decrease. In the subcortical network, estradiol (*Estimate* = 0.006, *SE* = 0.003, $p = 0.026$), progesterone (*Estimate* = 0.000, *SE* = 0.000, $p = 0.029$), and the interaction (*Estimate* = − 0.000, *SE* = 0.000, $p = 0.002$) shows significant effects. These results suggest

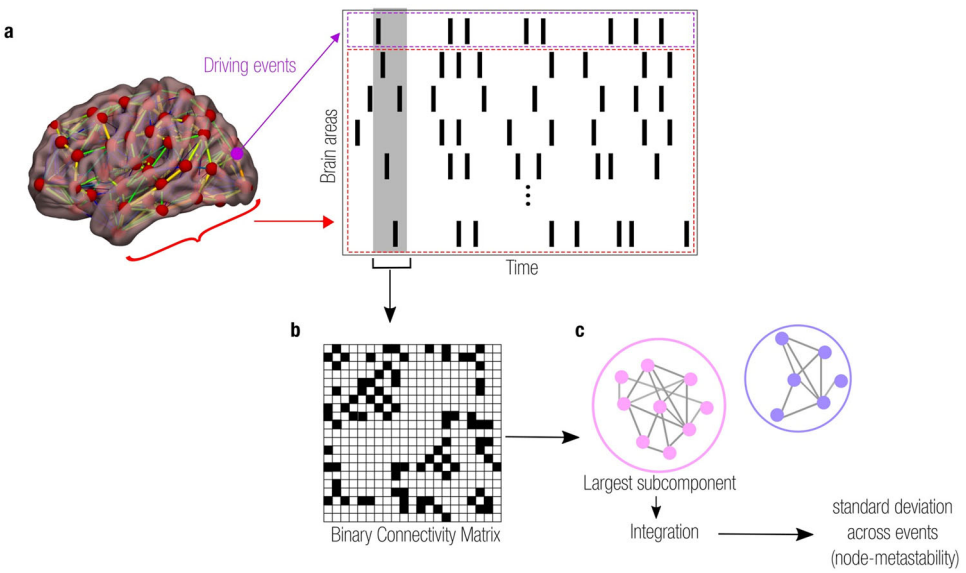

Fig. 2 | Intrinsic ignition framework. a Events were captured applying a threshold method[61] (see purple area). For each event elicited (gray area), the activity in the rest of the network was measured in the time window of 4TR (see red area). **b** A binarized matrix was obtained, representing the connectivity between brain areas where activity was simultaneous. **c** Applying the global integration measure[62], we obtained the largest subcomponent. Repeating the process for each driving event, we calculated the node-metastability computed as the standard deviation of the integration of each brain area over time. Figure adapted from[25,29,30].

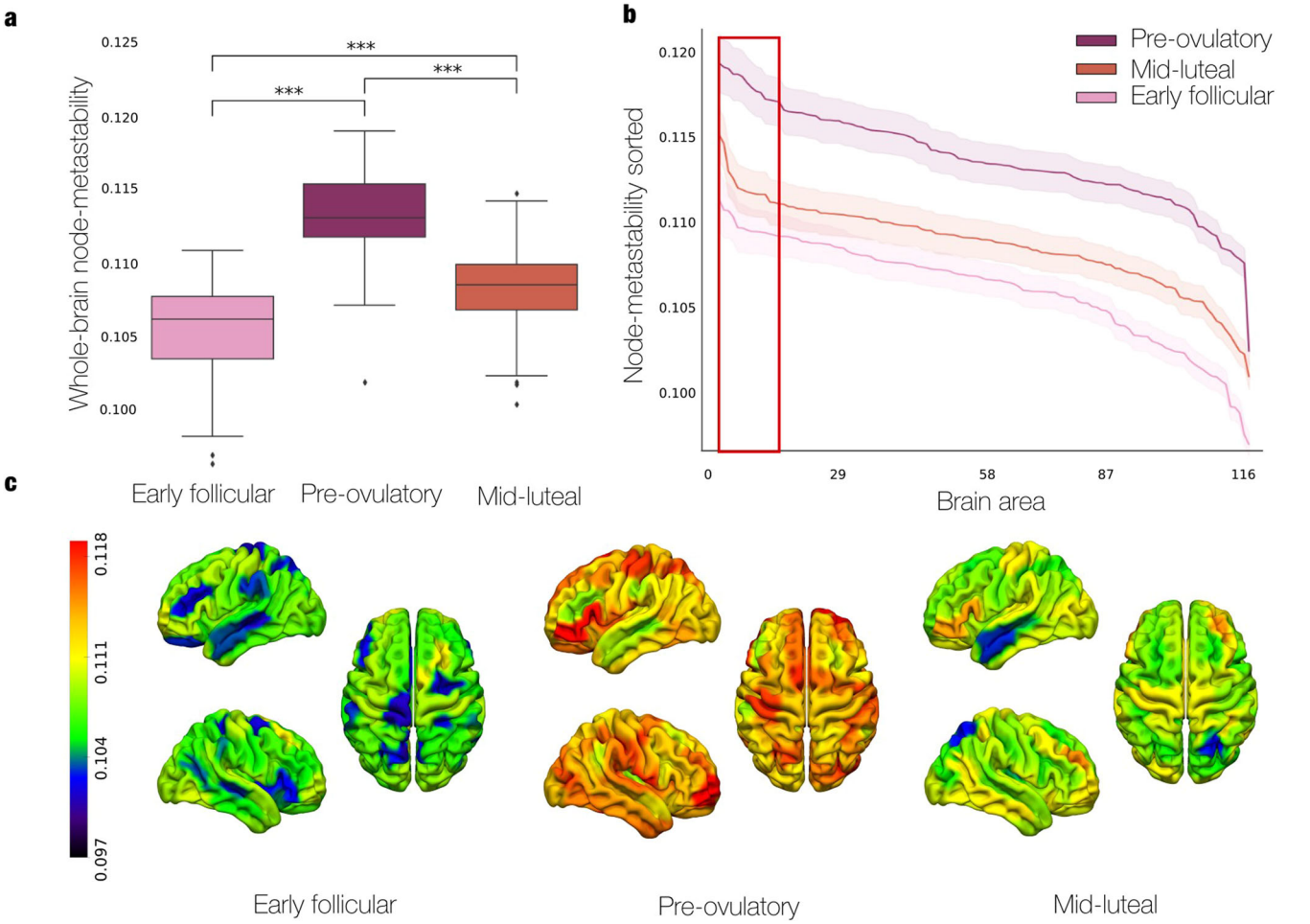

Fig. 3 | Dynamical complexity of menstrual cycle phases. a Whole-brain node-metastability. The pre-ovulatory phase showed higher node-metastability values across the whole-brain network than the early follicular and mid-luteal phases. *P*-values are based on Monte-Carlo permutation tests and were FDR corrected, *** represents $p < 0.001$. The box in the boxplot indicates the upper and lower quartiles and the line inside the box indicates the median. **b** Hierarchy. The red area marks the ten regions showing the highest node-metastability values in each phase. For the early follicular phase, brain areas showing the highest values were primarily located in the salience, DMN, dorsal attention, visual, and somatomotor networks. For the pre-ovulatory phase, the brain areas belonged to the DMN, limbic, subcortical, dorsal attention and control networks. During the mid-luteal phase, they were located in the subcortical, DMN, dorsal attention and control networks. **c** Renders brains represent the node-metastability values of the 116 areas for each menstrual cycle phase. The dynamical complexity of the pre-ovulatory phase across the whole-brain networks is clearly more complex than the dynamical complexity of the other two phases.

higher metastability in the subcortical network when estradiol increases and progesterone decreases or vice versa.

Discussion

In this study, we investigated the dynamical complexity underlying three menstrual cycle phases (i.e., early follicular, pre-ovulatory, and mid-luteal) in a sample of 60 healthy naturally-cycling women. First, the pre-ovulatory phase showed the highest metastability across the whole-brain functional network, followed by the mid-luteal and early follicular phases. Furthermore, our results revealed that the dynamical complexity of resting-state networks varies according to the menstrual cycle phase. Additionally, we found that age impacts the whole-brain functional network, control, and dorsal attention networks and that estradiol and progesterone modulate the whole-brain, DMN, limbic, dorsal attention, somatomotor and subcortical networks.

At the whole-brain network, we found that the dynamical complexity showed the highest variability over time (i.e., higher metastability) during the pre-ovulatory phase, followed by the mid-luteal, whilst the early follicular showed the lowest. Higher metastability across the network indicates higher dynamical complexity, implying that the network's activity exhibits more variability over time[26,29,30]. Only a few menstrual cycle fMRI studies applied a whole-brain dynamic approach and were based on the same dense-sampling single-subject dataset. Specifically, it has been observed that estradiol levels impact the DMN and the dorsal attention network, while progesterone was related to reduced coherence across the whole brain[11]. Furthermore, brain dynamics are more flexible among prefrontal, limbic, and subcortical nodes during the ovulatory phase (when estradiol levels peak)[12]. Similarly, it has been shown that whole-brain turbulent dynamics change between early follicular and luteal phases. In particular, the luteal phase showed more complex whole-brain turbulent dynamics across long distances in the brain, while the follicular phase was associated with more stable turbulent dynamics[23]. In addition, recurring network states of high-amplitude dynamic functional connectivity have been linked to fluctuations in follicle-stimulating and luteinizing hormones[24]. Such studies have shown that the menstrual cycle and hormone concentrations impact whole-brain dynamics. These studies however were based on the same single-subject dataset, which poses some limitations, related to inter-individual differences in brain activity patterns depending on age, hormone sensitivity, or expression of sex hormone receptors[8]. As such, the generalization of these findings may be limited. Additionally, the few fMRI time points in the pre-ovulatory phase of this dataset limit

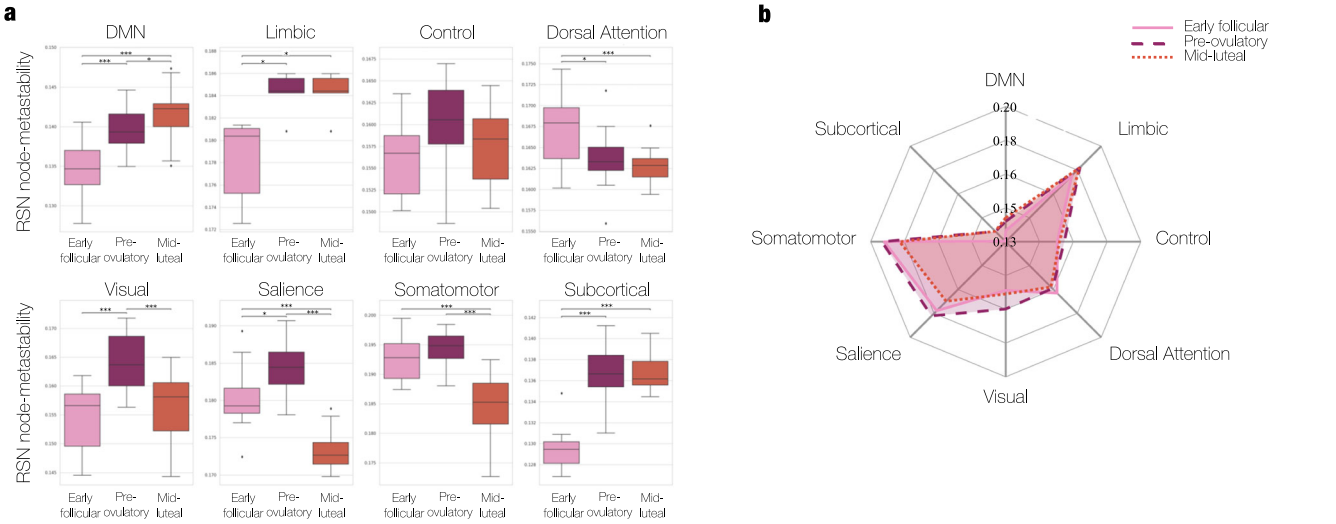

Fig. 4 | Node-metastability within resting state networks. a Compared to the early follicular phase, node-metastability was significantly increased in the pre-ovulatory and mid-luteal phases in the DMN, limbic, visual, and subcortical networks but lower in the dorsal attention network. Compared to the pre-ovulatory phase, the mid-luteal phase showed lower node-metastability in the visual, salience, and somatomotor networks and increased node-metastability only in the DMN. *P*-values are based on Monte-Carlo permutation tests and were FDR corrected, * denotes $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$. The box in the boxplot indicates the upper and lower quartiles and the line inside the box indicates the median. **b** The radar plot represents the average metastability values per resting state network for each menstrual cycle phase.

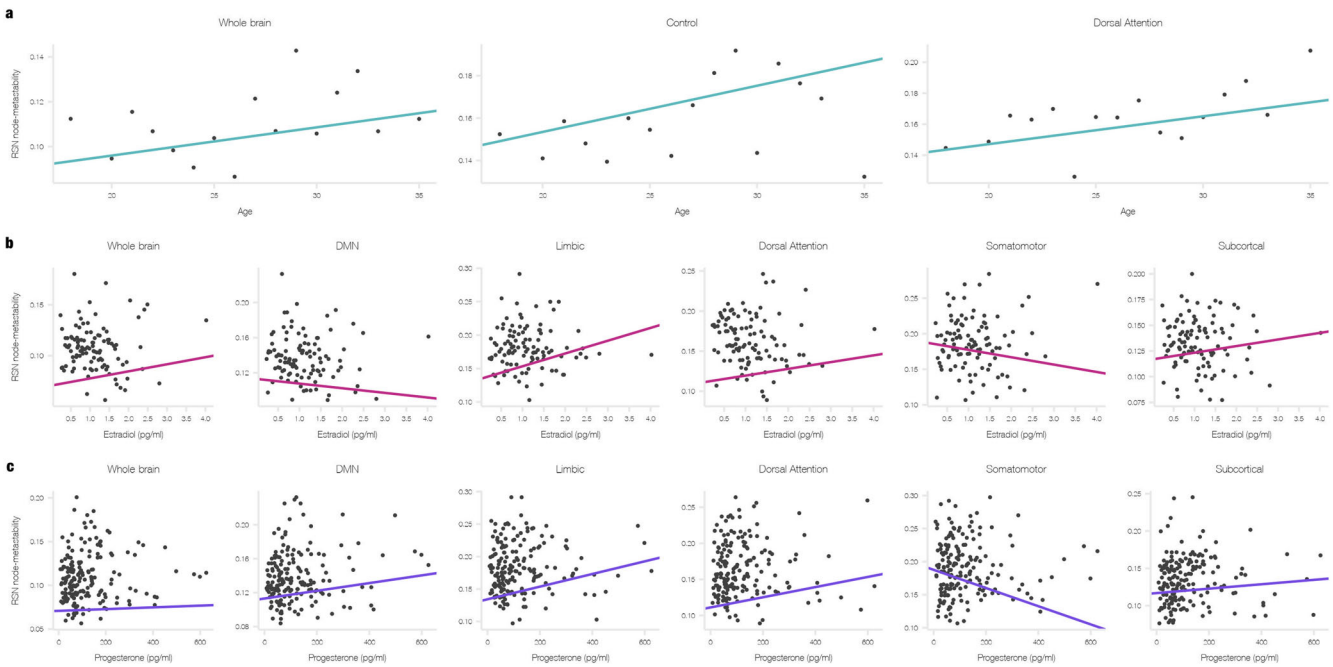

Fig. 5 | Multilevel models of the effects of age and ovarian hormone levels on brain networks. Points represent the observed data, and lines represent the multilevel model-implied intercepts (mean of model coefficients estimates for the random effect of subjects) and slopes (model coefficients estimates for the fixed effects of age, estradiol and progesterone). **a** Effect of age (in light blue) on node-metastability values at the whole-brain ($p = 0.033$), control ($p = 0.002$) and dorsal attention networks ($p = 0.011$). In these three cases, higher age predicted higher node-metastability values. **b** Significant effects of estradiol levels (in magenta) on node-metastability values at the whole-brain network ($p < 0.001$), on the default mode ($p = 0.022$), limbic ($p < 0.001$), dorsal attention ($p = 0.021$), somatomotor ($p = 0.011$), and subcortical networks ($p = 0.026$). In all cases, except for the default mode and somatomotor networks, higher estradiol levels predicted higher node-metastability values. **c** Significant effect of progesterone levels (in violet) on node-metastability values at the whole-brain network ($p = 0.028$), default mode ($p < 0.001$), limbic ($p < 0.001$), dorsal attention ($p < 0.001$), somatomotor ($p < 0.001$), and subcortical networks ($p = 0.029$). In all cases, except for the somatomotor network, higher progesterone levels predicted higher node-metastability values.

statistical power when comparing menstrual cycle phases. Our investigation aligns with and extends these findings by examining a large cohort of 60 healthy women during three menstrual cycle phases.

Our findings further reveal a phase-dependent dynamical complexity across large-scale resting-state networks. In particular, we found that most networks reached the highest complexity during the pre-ovulatory and mid-luteal phases. The only exception was for the dorsal attention network, which exhibited the highest complexity during the early follicular compared to the pre-ovulatory and mid-luteal phases. Specifically, the pre-ovulatory phase showed the highest dynamical complexity in visual, salience, and

somatomotor networks compared to the mid-luteal phase. Importantly, the dynamical complexity of the DMN increased significantly across phases (from the early follicular to pre-ovulatory to mid-luteal), with the peak occurring during the mid-luteal phase. This result aligns with our prior biphase investigation, which compared the follicular and luteal phases and revealed that the DMN exhibits higher levels of turbulent dynamics during the luteal phase in one naturally-cycle healthy woman[23]. Our current findings not only corroborate this result but also expand it by showing that this effect persists across all three menstrual cycle phases in a cohort of 60 healthy women. Additionally, we observed more complex dynamics within limbic and subcortical networks around ovulation and during the mid-luteal phase, which is consistent with prior menstrual cycle resting-state fMRI research[12,17]. Furthermore, our results also align with our previous publications, where we observed distinct brain dynamic patterns within the triple network model (i.e., DMN, salience, and control networks) across menstrual cycle phases[16], as well as a decrease in the motor network in the mid-luteal phase compared with the early follicular and pre-ovulatory phases[17]. Overall, these results demonstrate dynamical complexity changes related to menstrual-cycle phases across large-scale brain networks.

In order to effectively study the effects of the menstrual cycle on brain function, it is important to use repeated measures designs that account for within-person cycle phase and/or hormone effects[33–35]. Therefore, we used a mixed-effects model to examine the effects of age and hormones on metastability across the whole-brain and resting state networks. Our results revealed that age significantly increases whole-brain dynamics. Furthermore, we observed age-related effects in the control and dorsal attention networks. These findings are consistent with previous studies reporting a maximum peak in network efficiency around 40 years old, suggesting an increase in brain dynamics during early adulthood[30,36–39]. Notably, not only age but also ovarian hormones contribute to increased dynamic complexity across the whole-brain network. Our results suggest that low levels of both hormones are associated with reduced whole-brain dynamical complexity. Remarkably, an increase in progesterone is linked to high dynamical complexity, while an increase in estradiol is linked with the highest dynamical complexity. Our study comprises healthy women aged 18–35 years, and future investigations could extend this analysis to critical hormonal states such as menopausal transition and menopause. This would enhance our understanding of how ovarian sex hormones modulate brain dynamics throughout women's lifespans. Furthermore, we observed estradiol and progesterone-related changes in the dynamical complexity of resting-state networks, particularly in the DMN, limbic, dorsal attention, somatomotor, and subcortical networks. Specifically, we found that increased progesterone is associated with higher dynamical complexity in the DMN. Previous investigations have shown that both hormones impact connectivity within the DMN and between the DMN and other brain networks, influencing network efficiency and connectivity[11,16]. Higher progesterone levels have also been linked to an increased focus on others, potentially associated with the involvement of the DMN in self-referential mental processes[40]. Regarding the limbic network, our findings indicate that higher estradiol and progesterone predict increased dynamical complexity. The limbic network, comprising the orbitofrontal cortex (OFC) and the temporal lobe, plays a crucial role in emotional stimuli representation and processing[41]. Previous studies have linked OFC activity modulation to emotional processing across the menstrual cycle[42]. Another essential part of the limbic network is the temporal pole, located in the anterior part of the temporal lobe[43]. Recent evidence has shown that progesterone impacts the medial temporal lobe volume along the menstrual cycle[10,44]. Moreover, we found that the dynamical complexity of the dorsal attention network is modulated by estradiol and progesterone. It has been observed that estradiol enhances global efficiency within the dorsal attention network, influencing network connectivity[11] and that high progesterone levels are associated with increased turbulence dynamics in the dorsal attention network[23]. Our results also revealed a significant decrease in dynamical complexity in the somatomotor network when progesterone increases, especially in interaction with decreased estradiol, which aligns with previous investigations. Arelin et al.[14] provided evidence of endogenous progesterone modulation of functional connectivity within the somatomotor network. Additionally, eigenvector centrality analysis revealed a negative correlation between progesterone levels and functional connectivity in the sensorimotor resting-state network[11]. Similarly, a reduction in motor network activity during the luteal phase, characterized by increased progesterone, was observed compared to the early follicular and pre-ovulatory phases[17]. Finally, our findings revealed that increased estradiol levels and decreased progesterone, or vice versa, are associated with increased dynamical complexity in the subcortical network. Elevated estradiol levels have been associated with increased gray matter volumes in the bilateral hippocampus, while high progesterone is related to a significant increase in gray matter volumes in the right basal ganglia[45]. Hormonal variations throughout the menstrual cycle, influenced by estradiol and progesterone, impact functional connectivity in the hippocampus, caudate, and putamen-thalamic connectivity across different phases[18]. Overall, these findings evidence the significant modulatory role of ovarian hormones on dynamical complexity across large-scale resting-state networks.

Menstrual cycle neuroimaging studies have found that ovarian hormones modulate network dynamics during a natural menstrual cycle[11,12,23]. However, Syan et al.[46] used seed-based and independent component analysis and reported no significant differences in resting state networks between the follicular and luteal phases but found correlations between sex hormones and patterns of functional connectivity in both menstrual cycle phases. Liparoti et al.[47] applied the concept of avalanche (i.e., variations of the functional brain repertoire) using magnetoencephalography. Specifically, they found that the brain's flexibility increases during the peri-ovulatory phase but did not find any association between sex hormones and the observed avalanche patterns. Thus, they observed an effect of phase but not of ovarian hormones. Here, we observed that menstrual cycle phases and ovarian hormones modulate brain dynamics. This discrepancy in findings highlights the complexity of studying the relationship between brain networks and the menstrual cycle. Therefore, further studies are needed to understand better the underlying mechanisms and potential factors contributing to these inconsistent results.

We want to acknowledge some limitations. This study applied a model-free approach; thereby, it did not provide insights into the brain mechanisms of the menstrual cycle. Theoretical whole-brain models that simulate brain dynamics can help to reveal the mechanistic principles underlying menstrual cycle brain activity changes[48,49]. Furthermore, evidence has shown that the results in functional magnetic resonance imaging studies on brain networks can vary depending on different analysis pipelines[50] and the atlas used[51,52]. Moreover, utilizing a higher magnetic field strength and decreasing the repetition time during scanning can enhance sensitivity and resolution and may offer more comprehensive insights into functional brain networks. Finally, while saliva sampling provides a non-invasive method, it is important to recognize that concentrations of hormones in saliva may differ from those in blood, which can affect the accuracy of the results[35,53].

In summary, our study sheds light on the intricate interplay between menstrual cycle phases, hormone levels, age, and brain network dynamics. This study demonstrates that the menstrual cycle phases modulate the dynamical complexity of the whole-brain functional network as well as large-scale resting-state networks. Our results also confirmed the impact of age and hormone levels on brain dynamics. Further investigations are needed to determine inconsistent results due to methodological differences among studies. This field of research may have implications for elucidating the effects of hormones on cognition, mood, and behavior in healthy women and those affected by menstrual cycle-related disorders.

Methods

Participants

A total sample of 60 healthy young women was selected from a dataset previously described in Hidalgo-Lopez et al.[16]. The study was conducted on women between the ages of 18 and 35 who had regular menstrual cycles lasting 21–35 days with intercycle variability of fewer than 7 days. All participants met the following inclusion criteria: (1) not having used hormonal contraceptives in the 6 months before the study, (2) having no history of

neurological, psychiatric, or endocrine disorders, and (3) not taking any medications. Three appointments were scheduled for each participant: during the early follicular phase (1–7 days after the onset of current menses), in the pre-ovulatory phase (2–3 days before the expected date of ovulation), and during the mid-luteal phase (3 days after ovulation to 3 days before the expected onset of next menses). The order of appointments was counterbalanced to minimize any potential bias. The pre-ovulatory sessions were confirmed by commercial urinary ovulation tests (Pregnafix ®). Participants were asked to confirm the onset of the following menses after the appointment. The cycle duration was calculated based on the participants' self-reported onset dates of their last three periods. Participants gave informed written consent to participate in the study. The University of Salzburg's ethics committee approved the study and conformed to the Code of Ethics by the World Medical Association (Declaration of Helsinki).

Hormone analysis

Hormone levels were assessed using Salimetrics salivary Estradiol and Progesterone ELISAs. Saliva samples were collected from participants using the passive drool method, stored at −20° until analysis, and centrifuged twice at 3000 rpm for 15 and 10 min, respectively, to remove solid particles. All samples were tested in duplicates, and samples with more than 25% variation between duplicates were re-analyzed.

MRI data acquisition

MRI images were acquired using a Siemens Magnetom TIM Trio 3T scanner. The high-resolution T1-weighted images were acquired with 160 sagittal slices (slice thickness = 1 mm; TE = 291 ms; TR = 2300 ms; TI delay = 900 ms; (FA) 9°; FOV 256X256 mm). Resting-state fMRI was performed using a T2* weighted gradient echo-planar (EPI) sequence with 36 transversal slices (≈9 min, volumes = 244; TE = 30 ms; TR = 2250 ms; flip angle (FA) 70°; slice thickness = 3.0 mm; matrix 192 × 192; FOV 192 mm; in-plane resolution 2.6 × 2.6 mm). During the resting state, participants were instructed to relax, close their eyes, and let their minds flow.

Preprocessing

For each participant, the first six volumes were discarded, and the functional images were despiked using the 3d-despiking algorithm implemented in AFNI[54–56]. Then, despiked images were pre-processed using standard procedures and templates in SPM12 (www.fil.ion.ucl.ac.uk/spm), including segmentation of the structural images using CAT12. The resulting images were then subjected to the ICA-AROMA algorithm implemented in FSL to remove artefactual components in a non-aggressive manner[57,58]. BOLD time series were filtered within the narrowband (0.01–0.09 Hz). Pre-processing quality control procedures included the automatic exclusion of participants with excessive movement (>3 mm translation, >2° rotation), visual inspection of structural and functional scans ensuring adequate coregistration, and visually checking the normalization to a standard T1 and an EPI MNI template.

Brain parcellation

Time series were obtained using two brain atlases. The Schaefer cortical parcellation[59], which consists of 100 cortical regions clustered into 7 resting state networks (https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal), and the Tian subcortical parcellation[60], which consists of 16 subcortical regions, representing the subcortical network (https://github.com/yetianmed/subcortex).

Intrinsic ignition framework

We computed the Intrinsic Ignition Framework[25] to evaluate the effect of intrinsic local perturbations (i.e., neural events), reflecting the capacity of a brain area to propagate neural activity to other brain areas. Our evaluation of each area's node-metastability was measured as the standard deviation of integration over time. In other words, this framework quantifies the degree of whole-brain integration from spontaneously occurring events over time. Figure 2 schematizes the methodology for obtaining the intrinsic integration across brain areas. The algorithm captures driving events for each brain area, which are transformed into a binary signal using a threshold[61]. To represent events as a binary signal, time series are transformed into z-scores, denoted as $z_i(t)$, and a threshold value, θ, is applied. Specifically, an event is marked as 1 in the binary sequence $\sigma(t)$ if $z_i(t)$ exceeds the threshold from below and marked as 0 otherwise. When a brain area triggers an event, neural activity is measured in all brain areas within a set time window of 4TR. A binary matrix is then constructed to represent the connectivity between brain areas exhibiting simultaneous activity. The measure of global integration[62] is applied to determine the broadness of communication across the network for each driving event (i.e., the largest subcomponent). This process is repeated for each spontaneous neural event to obtain the node-metastability (measured as the standard deviation of the integration over time) for each brain area across the network, where higher node-metastability corresponds to higher dynamical complexity. Thus, each brain area can be classified according to its local degree of functional variability, i.e., local- or node-metastability. In other words, different levels of temporal diversity in a given node can be considered a measure of local functional variability or metastability and thus describe the versatility of a given node within the network. This analysis was assessed across the whole brain and within specific resting-state networks for each woman in each menstrual cycle phase.

Statistical analyses

For the hormone analysis, we fitted two independent linear mixed models. In particular, we included estradiol or progesterone as a dependent variable, the cycle phase (i.e., early follicular, pre-ovulatory, mid-luteal) as a fixed effect, and the participant number (subject) as a random effect. We defined the syntax for the models as: $hormone \sim menstrualCyclePhase + (1|subject)$. For the intrinsic ignition framework, we applied the Monte Carlo permutation method (10,000 iterations) to evaluate the outcomes of the node-metastability between each pair of phases. Furthermore, we corrected p-values using the False Discovery Rate (FDR) method[63] to account for multiple comparisons when comparing menstrual cycle phases. The intrinsic ignition framework, Monte Carlo permutation and FDR were performed using Matlab version 2023a (MathWorks, Natick, MA, USA). Moreover, we carried out mixed-effect multilevel models to study the effects of estradiol and progesterone levels and age on node-metastability at the whole brain network and within resting state networks. Furthermore, we also included age as an independent variable, given it is an important factor affecting hormonal patterns[64,65]. As dependent variable, we included a vector with all node-metastability values of each specific network for each woman ($n = 60$) in each menstrual cycle phase ($n = 3$). Specifically, the dependent variable (AllNodesMetastability) for the mixed-effect statistical model of the whole-brain network comprised a vector of 116 node-metastability values. Additionally, the models for the resting state networks included a vector of 24 node-metastability values for the DMN, limbic (5 values), control (13 values), dorsal attention (15 values), visual (17 values), salience (12 values), somatomotor (14 values), and subcortical (16 values). As fixed effects, we included the age, progesterone, estradiol, and the interaction between progesterone and estradiol, and subject as random effect. We defined the models syntax as: $AllNodesMetastability \sim 1 + age + estradiol + progesterone + estradiol * progesterone + (1|subject)$. We included age, hormone values, and node-metastability values in all multilevel models as intra-subject variables. We performed all multilevel model analyses using R Statistical Software (v4.3.2; ref. [66] with the package lme4[67].

Data availability

The dataset analyzed during the current study is available from the corresponding authors upon reasonable request.

Code availability

Scripts are openly available online on https://github.com/aescrichs/menstrualcycle-ignition.

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Conceptualization: D.A. and A.E. Methodology: G.D. and A.E. Data analysis: D.A., P.D., I.A., E.A. and A.E. Visualization: D.A., P.D., I.A., E.A. and A.E. Supervision: B.P. and A.E. Data preprocessing: E.H.-L. and B.P. Data curation: E.H.-L., B.P. and A.E. Writing—original draft: D.A. and A.E. Writing—review & editing: all authors.

Competing interests

The authors declare no competing interests.

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