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Hormonal Modulation of Brain Control Energy Across the Menstrual Cycle: A Network Control Theory Study

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Abstract

Extensive research shows the menstrual cycle shapes brain structure and function, yet these domains are typically studied separately. To bridge this gap and illuminate the structure-function link driving female brain dynamics, this study applied Network Control Theory across two primary analyses. First, by combining daily functional states from the 28andMe dataset with structural connectomes from the Hormone Health Study, we computed daily control energy. The natural cycle produced six control energy peaks that exceeded the 95% reference range of the oral contraceptive (OC)-stabilized window, demonstrating that endogenous hormones amplify day-to-day neural control costs. Second, we analyzed transition energies among 123 meta-analytic cognitive states across cycle phases. Exploratory K-means clustering identified three distinct phase-dominant profiles: perceptual and semantic states stabilized during the follicular phase, executive and motor states stabilized during the luteal phase, and higher-order control states remained invariant. Taken together, the natural menstrual cycle amplifies daily neural energy requirements and dynamically reconfigures the transition costs between cognitive states across phases, whereas OC use flattens this energetic variability. These findings highlight the critical need for sex- and phase-specific neurobiological models to accurately understand female brain dynamics and advance

women's brain health.

Keywords

Menstrual cycle, Brain state transition, Network control theory, Hormonal modulation

Introduction

The human brain is a dynamic endocrine organ, undergoing structural and functional remodeling in response to the periodic fluctuations of ovarian hormones [1-3]. A typical menstrual cycle spans approximately 30 days and is characterized by systematic shifts in pituitary gonadotropins—follicle-stimulating hormone (FSH) and luteinizing hormone (LH)—and ovarian sex steroids, namely estradiol and progesterone. Decades of research spanning animal models and human neuroimaging have established the impact of these hormones on the brain and behavior. In humans, this includes structural variations such as volumetric changes in the hippocampus [4-6], altered activation patterns during task functional magnetic resonance imaging (fMRI) [1], and the dynamic reconfiguration of white matter integrity and large-scale functional networks observed through resting-state fMRI [7-13]. While existing resting-state fMRI studies have successfully applied a network perspective to reveal phase-dependent shifts in functional connectivity, they have largely examined these functional networks independently of the brain's physical wiring [10]. This compartmentalization may not fully capture the extent to which functional brain dynamics are intrinsically constrained by the underlying anatomical architecture. Consequently, how hormonal variations reconfigure the brain's unified structure-function architecture across the menstrual cycle remains a critical open question. It is this explicit structure-function link that the present study seeks to illuminate.

To bridge this gap, we employ Network Control Theory (NCT), a framework derived from classical control theory and network science that directly integrates physical network topology with functional system dynamics [14]. Specifically, NCT provides a quantitative approach to estimate the theoretical energy required for transitions between distinct functional brain states, as dictated by the underlying structural connectome [15]. Through this, NCT offers a powerful framework for uniting anatomical connectivity and functional state transitions within a single system-level model. Since its introduction to neuroscience, NCT has been successfully applied to elucidate the energetic costs of high-order cognitive transitions, neurodevelopmental maturation, and the inefficiencies associated with neurological disorders such as schizophrenia and dementia [16-18]. By assessing the optimal control energy required to drive the system from an initial state to a target state, we can effectively estimate the computational cost of neural flexibility.

Leveraging this framework, the present study provides a multi-level investigation into the hormonal modulation of brain dynamics using two complementary datasets. First, to evaluate how the choice of structural connectome influences the estimation of control energy, we compared biologically individualized, phase-specific connectomes from 22 female participants in the Hormone Health Study (HHS) with a standardized, phase- and sex-nonspecific population template from the Human Connectome Project-Young Adult (HCP-

YA) [13,19,20]. Onto these connectomes, we mapped daily functional brain states from the densely sampled, longitudinal, single-subject 28andMe dataset to track day-by-day fluctuations in control energy across one natural menstrual cycle and one oral contraceptive (OC) cycle [12,21]. To accurately capture these daily states within the NCT framework, we utilized the Synergy-Redundancy (SR) gradient derived from resting-state fMRI. As detailed in the Methods, unlike conventional metrics, the SR gradient effectively isolates inter-regional information flow from self-referential signals, making it uniquely suited for NCT [22,23]. By utilizing the 23-day OC cycle as a hormonally suppressed baseline, we compared it directly against the natural cycle to test whether endogenous hormonal fluctuations drive day-to-day variability in neural control costs. Second, to extend our findings beyond general resting-state dynamics and investigate phase-specific cognitive reorganization, we projected 123 meta-analytic cognitive activation maps from Neurosynth onto the HHS phase-specific connectomes [24,25]. Within the natural cycle context, we quantified inbound and outbound transition energies and compared them between the follicular and luteal phases to identify cognitive domains with distinct, phase-sensitive energy profiles.

By conducting parallel investigations into high-resolution single-subject dynamics and broad meta-analytic cognitive states, this study aims to provide a comprehensive, system-level account of how the menstrual cycle reconfigures the governing principles of human brain dynamics and cognitive flexibility. Ultimately, by mapping these theoretical energetic reconfigurations, this work establishes a biologically informed baseline that highlights the importance of integrating dynamic neuroendocrine parameters into computational models of the human brain.

Methods

Ethics declarations

The data used in this study are publicly available for research purposes. All original data collection for the 28andMe and HHS datasets were approved by the University of California, Santa Barbara Institutional Review Board/Human Subjects Committee, with written informed consent obtained from all participants by the primary investigators [12,13]. The HCP-YA study was approved by the Washington University in St. Louis Institutional Review Board [26].

Network control theory framework

NCT was applied to quantify the energetic cost of transitions between brain states using individual structural connectomes derived from diffusion MRI data [15,27]. This framework models the brain as a continuous-time linear time-invariant dynamical system and estimates the optimal control energy required to drive the system from an initial state to a target state within a specified time horizon [27]. By assessing not only whether network topology differs but also how much additional energy is necessary to achieve functional transitions, NCT provides a systems-level bridge between structural connectivity and cognitive function. To estimate the energy required to steer brain dynamics between cognitive states, brain dynamics were modeled as:

$$\frac{dx(t)}{dt} = Ax(t) + Bu(t)$$

where A is the structural connectome, B is the control set, $x(t)$ is the state vector representing the activity level of brain regions at time t , and $u(t)$ is the external control input applied to the system. We calculated the minimum control energy required to drive the system from an initial state x_0 to a target state x_f over a finite time interval T , with T set to 1, representing a normalized time unit for continuous-time transitions as standard in macroscale brain network models. To maintain system stability, each structural connectome A was normalized according to its largest eigenvalue magnitude prior to the analysis:

$$A_{norm} = \frac{A}{c + \lambda_{max}} - I, \lambda_{max} = \max(|\lambda_i|), \forall \lambda_i \in eig(A)$$

where c is a constant, set to 1 in this study, and I is the identity matrix. The control energy required to transition the system is estimated by minimizing a cost function J . This function balances the precision of the state trajectory and the magnitude of the control effort:

$$J = \int_0^T [||u(t)||^2 + \rho ||S(x(t) - x_r)||^2] dt$$

The cost function employs a regularization parameter, $\rho > 0$, to balance the trade-off between minimizing control energy and reducing trajectory deviation. In this study, the regularization parameter ρ was set to 1. The diagonal weighting matrix S identifies specific brain regions for penalization, while x_r represents the target reference state (typically a zero vector). In cases where $x_r = 0$ and $S = I$, the cost is calculated based on how much neural activity across all regions deviates from a baseline of zero. The optimal control trajectory was determined by formulating a joint state-costate system through the Hamiltonian framework:

$$\frac{d}{dt} \begin{bmatrix} x(t) \\ \lambda(t) \end{bmatrix} = M \begin{bmatrix} x(t) \\ \lambda(t) \end{bmatrix} + c$$

where $\lambda(t)$ is the costate vector, and the joint system matrix M and a constant vector c are characterized as follows:

$$M = \begin{bmatrix} A_{norm} & -\left(\frac{1}{2\rho}\right)BB^T \\ -2S & -A_{norm}^T \end{bmatrix}, c = \begin{bmatrix} 0 \\ 2Sx_r \end{bmatrix}$$

The analytic solution for the system at time T is given by:

$$\begin{bmatrix} x(T) \\ \lambda(T) \end{bmatrix} = e^{MT} \begin{bmatrix} x_0 \\ \lambda_0 \end{bmatrix} + (e^{MT} - I)M^{-1}c$$

The matrix exponential e^{MT} was first evaluated and then decomposed into four constituent blocks:

$$e^{MT} = \begin{bmatrix} E_{11} & E_{12} \\ E_{21} & E_{22} \end{bmatrix}$$

The initial costate λ_0 was determined using the following relation:

$$\lambda_0 = E_{12}^{-1}(x_f - E_{11}x_0 - [(E_{11} - I)E_{12}]c)$$

To reconstruct the complete state trajectory, we performed a numerical simulation of the joint system dynamics over the interval $[0, T]$ with a discretized time step of $\Delta t = 0.001T$. At each iteration, the system state was updated as follows:

$$z(t + \Delta t) = A_d z(t) + B_d$$

where $z(t) = [x(t); \lambda(t)]$, $A_d = e^{M\Delta t}$, and $B_d = (A_d - I)c$. Following the system simulation, the optimal control inputs were determined as follows:

$$u(t) = -\left(\frac{1}{2\rho}\right)B^T \lambda(t)$$

The optimal control energy for each region is then calculated by integrating the squared control signal over the time horizon using Simpson's rule:

$$E = \int_0^T ||u(t)||^2 dt$$

The total energy required for a specific transition is the sum of energy across all regions, or the average energy depending on the specific analysis context. These analyses were implemented in Python using the nctpy package, which provides tools for simulating and analyzing network control processes in brain systems [27].

Structural connectomes generation

For the structural connectome in NCT, we utilized individual phase-specific connectomes from the HHS and a group-averaged connectome from the HCP-YA as a control [19,20,26]. The HHS comprises 22 healthy, naturally cycling young female participants who completed 3 MRI sessions: menses, ovulation, and mid-luteal [19]. These participants were drawn from a cohort (mean age = 21.73 years; range = 18–29) that encompassed a diverse demographic background, including White non-Hispanic/Latino, Hispanic/Latino, Black/African American, West Asian/Middle Eastern, East Asian, and Southeast Asian individuals. Per the study's rigorous inclusion criteria, all participants were between the ages of 18 and 30, nulliparous, and had a relatively regular menstrual cycle (cycle length of 21–40 days). To eliminate the confounding effects of exogenous hormones, participants were required to be completely free from hormonal or implant birth control for at least three months prior to study enrollment and must have never undergone hormonal therapy. Furthermore, participants were screened to ensure no clinically major reproductive, cardiovascular, neurological, or severe psychiatric conditions were present. MRI data were acquired using a Siemens 3T Prisma scanner equipped with a 64-channel phased-array head/neck coil. High-resolution T1-weighted MPRAGE anatomical scans were collected with the following parameters: repetition time (TR) = 2500 ms, echo time (TE) = 2.22 ms, inversion time (TI) =

851 ms, field of view (FOV) = 241 mm, flip angle = 7°, and a voxel size of 0.9 mm³. Diffusion MRI data were acquired using Q-space trajectory imaging sequences, which are optimized for a high contrast-to-noise ratio. The diffusion protocol included a series of four spherical b-tensors (b = 0, 100–500, 1000, 1500 s/mm²; 3 diffusion directions) and four linear b-tensors (b = 500, 1000, 1500, 2000 s/mm²; 6, 10, 16, and 30 diffusion directions). Sequence parameters included TR = 6308 ms, TE = 80 ms, maximum diffusion gradient amplitude = 80.0mT/m, FOV = 230 mm, flip angle = 90°, in-plane resolution = 2.0 × 2.0 mm², and a slice thickness of 4.0 mm.

For each participant, individual structural connectomes were reconstructed for three estimated menstrual phases—menses, ovulation, and mid-luteal—using T1-weighted MRI and multidimensional diffusion MRI acquired at each phase. Raw diffusion MRI data were processed through a comprehensive preprocessing pipeline, which included denoising, ringing artifact removal, and corrections for eddy current-induced distortions and head motion. To provide the anatomical priors necessary for Anatomically Constrained Tractography (ACT), T1-weighted structural images were co-registered to the diffusion space and segmented into five distinct tissue types [28]. To accurately resolve crossing fibers within the multidimensional diffusion data, we employed multi-shell multi-tissue constrained spherical deconvolution. Fiber orientation distributions were estimated separately for white matter, gray matter, and cerebrospinal fluid using group-averaged response functions, ensuring consistent quantification and comparability across all participants and menstrual phases. Whole-brain streamlines were subsequently generated using a probabilistic algorithm, producing 20 million streamlines per session. The ACT framework was strictly applied to ensure that streamline seeds and terminations were biologically constrained to the appropriate tissue interfaces. To enhance the biological validity of the reconstructed connectomes and mitigate the inherent over-fitting of traditional tractography, the Spherical-Deconvolution Informed Filtering of Tractograms algorithm was applied [29]. This approach assigned individual weights to each streamline, effectively matching streamline densities with the underlying diffusion signal. Finally, all structural connectomes were parcellated according to the Schaefer 100-region cortical atlas to maintain consistent node definitions across datasets. This procedure yielded a weighted adjacency matrix for each of the three menstrual phases per participant, representing the structural connectivity architecture. MRI preprocessing and tractography were performed using the MRtrix software suite [30].

Analysis 1: Daily control energy dynamics across hormonal conditions using a dense-sampling, single-subject resting-state fMRI dataset (28andMe)

The 28andMe study

To investigate day-by-day brain state using resting-state fMRI, we utilized data from the 28andMe study [12,21]. The 28andMe study involved a single 23-year-old Caucasian female participant with a history of regular 26–28-day menstrual cycles and no prior neuropsychiatric diagnoses or endocrine disorders. The study was conducted over two consecutive 30-day periods. The first 30-day section captured a natural menstrual cycle (drug-free condition), while the second 30-day section—conducted one year later—captured a hormonally suppressed cycle during OC use. The participant had been taking a combined oral contraceptive formulation (0.02 mg ethinyl estradiol, 0.1 mg levonorgestrel; Aubra, Afaxys Pharmaceuticals) for 10 months prior to the start of the OC data collection. The OC

section consisted of 23 days on active pills followed by 7 days on placebo. As reported in the original study, the participant experienced no substantial adverse shifts in mood, sleep quality, or selective attention between the natural and OC cycles, indicating no severe behavioral side effects. Throughout the study, daily time-locked collection of serum and whole blood was performed at a consistent time each morning (10:00 AM $\pm$ 30 min in the natural cycle, and 11:00 AM $\pm$ 30 min in the OC cycle) following at least 2 hours of fasting, and daily MRI scans were acquired to minimize circadian confounding on both hormone concentrations and resting-state fMRI data.

For this densely sampled single-subject dataset, daily MRI scans were performed on a Siemens 3T Prisma scanner with a 64-channel phased-array head coil. To minimize head motion, the participant's head was secured using a custom 3D-printed foam head case. High-resolution T1-weighted MPRAGE anatomical scans were acquired (TR = 2500 ms, TE = 2.31 ms, TI = 934 ms, flip angle = 7°, 0.8 mm isotropic voxel size), followed by a gradient echo field map. Daily functional brain states were captured via a 10-minute resting-state fMRI scan using a T2*-weighted multiband echo-planar imaging (EPI) sequence sensitive to blood-oxygen-level-dependent (BOLD) contrast (72 oblique slices, TR = 720 ms, TE = 37 ms, voxel size = 2 mm³, flip angle = 52°, multiband factor = 8). Initial preprocessing of the functional data was conducted using SPM12. Scans were realigned and unwarped to correct for head motion and geometric deformations, then co-registered to the mean motion-corrected image and the high-resolution anatomical T1-weighted image. All daily scans were subsequently registered to a subject-specific anatomical template generated via ANTs multivariate template construction and smoothed using a 4 mm FWHM isotropic Gaussian kernel. Timeseries denoising was implemented which included global signal scaling, linear detrending, and regression of nuisance covariates. The nuisance regression model incorporated five physiological noise components and head motion modeled via the Friston-24 approach to account for autoregressive and nonlinear effects.

Deviation of the SR gradient from fMRI BOLD signals

Conventional functional brain state metrics, such as Pearson correlation, often conflate two distinct sources of fMRI signal: the externally driven influence exerted on a region by the rest of the network, and the region's own prior activity carried forward through temporal autocorrelation [31]. This conflation is particularly problematic for the NCT framework, which models brain dynamics as a linear time-invariant system in which each region's future state is driven by inputs propagated from other regions through the structural connectome [15,32]. To align the state representation with this causal architecture, we utilized the SR gradient as a brain state vector in NCT. This metric serves as a proxy for the daily brain state by quantifying the extent of external information integration while isolating it from self-referential signals [23]. While conventional connectivity metrics primarily capture statistical synchrony, the SR gradient, derived via information decomposition, explicitly maps the informational architecture of the brain [33]. It delineates a functional hierarchy ranging from redundancy-dominated sensorimotor regions to synergy-dominated trans-modal networks that integrate distinct signals for higher-order cognition [34]. Recent evidence demonstrates that this synergistic-redundant topography is not merely a static map, but a dynamically fluctuating brain state that continuously reconfigures over time [35]. This property suggests the SR gradient may be highly applicable to NCT, given that its defined target state broadly reflects the transient patterns of inter-regional information flow hypothetically supported by

272 underlying structural connectivity.

273 To quantitatively capture these dynamic patterns of information integration from empirical
 274 BOLD signals, we frame our analysis within an information-theoretic perspective. The
 275 foundation of this approach relies on the concept of entropy, which quantifies the uncertainty
 276 associated with the state of a random variable X [33]. For a discrete random variable X
 277 taking value x from the set χ with a probability distribution $P(X = x)$, the Shannon
 278 entropy is defined as:

$$279 \quad H(X) = - \sum_{x \in \chi} P(x) \log_2 P(x)$$

280 In the context of continuous data, such as fMRI Blood-Oxygen-Level-Dependent (BOLD)
 281 signals, this is generalized to differential entropy:

$$282 \quad H(X) = \int_{x \in \chi} P(x) \log P(x) dx$$

283 The initial stage involves extracting BOLD time-series from a predefined parcellation of the
 284 brain. Given that BOLD data are continuous, we assume a multivariate Gaussian distribution
 285 with standard deviation σ to facilitate the application of differential entropy metrics. The
 286 entropy can be expressed as:

$$287 \quad H(X) = \frac{\ln(2\pi e \sigma^2)}{2}$$

288 Furthermore, for a multivariate Gaussian random variable $\mathbf{X} = \{X_1, X_2, \dots, X_N\}$, the joint
 289 entropy is determined by the determinant of its covariance matrix Σ :

$$290 \quad H^N(\mathbf{X}) = \frac{\ln[(2\pi e)^N |\Sigma|]}{2}$$

291 While mutual information is traditionally used to analyze interactions between bivariate pairs,
 292 characterizing higher-order interactions among three or more variables requires advanced
 293 metrics. One such measure is total correlation (TC), which is defined using the Kullback-
 294 Leibler divergence (D_{KL}):

$$295 \quad TC(\mathbf{X}) = \sum_{i=1}^N H(X_i) - H(\mathbf{X}) = D_{KL}(P(X_1, \dots, X_N) || \prod_{i=1}^N P(X_i))$$

296 TC quantifies redundant interactions, reaching higher values when the state of a single
 297 variable provides substantial information about the states of others. For continuous data, it is
 298 calculated as:

$$299 \quad TC^N(\mathbf{X}) = \frac{-\ln(|\Sigma|)}{2}$$

300 To further probe the functional structure, we introduce dual total correlation (DTC):

$$DTC(X) = H(X) - \sum_{i=1}^N H(X_i | \mathbf{X}^{-i})$$

where $H(X_i | \mathbf{X}^{-i})$ represents the residual entropy—the uncertainty in X_i that remains unresolved by all other variables in the set $\mathbf{X}$. DTC represents the entropy shared among at least two elements and increases as the system becomes more synchronized. The balance between redundancy and synergy within a system is captured by O-information, defined as the difference between TC and DTC:

$$\Omega(\mathbf{X}) = TC(\mathbf{X}) - DTC(\mathbf{X})$$

A positive value ($\Omega > 0$) indicates a redundancy-dominated state, whereas a negative value ($\Omega < 0$) signifies a synergy-dominated state. The complexity (C) of the system $\mathbf{X}$ can also be formulated by considering the expected versus actual reduction in correlation when a single element is removed:

$$C(\mathbf{X}) := TC(\mathbf{X}) - \frac{TC(\mathbf{X})}{N} - \mathbb{E}[TC(\mathbf{X}^{-i})]$$

There exists a formal relationship between DTC and complexity, such that:

$$DTC(\mathbf{X}) = N \times C(\mathbf{X})$$

Utilizing these identities, O-information can be computed solely through total correlation terms:

$$\Omega(\mathbf{X}) = TC(\mathbf{X}) - N \times C(\mathbf{X}) = (2 - N)TC(\mathbf{X}) + \sum_{i=1}^N TC(\mathbf{X}^{-i})$$

To identify the specific contribution of individual nodes to the collective higher-order structure, we define the O-information gradient. This is the change in the system's total O-information when a specific node is removed. The gradient reveals how higher-order dependencies are spatially and functionally organized across the complex neural system. For each node i , we calculate the difference between the O-information of the entire system $\mathbf{X}$ and the O-information of the subsystem $\mathbf{X}^{-i}$ excluding that node:

$$Gradient_i = \Omega(\mathbf{X}) - \Omega(\mathbf{X}^{-i})$$

This gradient quantifies the specific contribution of each brain region to the overall synergy-redundancy balance of the network. The calculated gradients are assigned to each brain region (using the Schaefer 100-parcel atlas) to characterize the daily SR gradient profile. This spatial distribution defines our brain state vectors for NCT, distinguishing between hub regions that manage redundant information and integrative regions that facilitate synergistic computation.

331 Cortical thickness as a heterogeneous control set in NCT

In NCT, the control set is a matrix that specifies the nodes receiving external control input to drive state transitions within the network [27]. Each element of this matrix can assign a weight to a given node, representing the extent to which that node contributes to the system's

dynamics under external input. In this study, we first employed a uniform full control set, represented as an identity matrix, if all brain regions contribute equally to network control. This configuration reflects the common assumption that the brain responds homogeneously to external input and is widely adopted in prior NCT studies.

However, to capture the regional heterogeneity of the brain's structural organization, we additionally implemented a heterogeneous control set derived from the participant's day-by-day cortical thickness maps obtained from T1-weighted MRI in the 28andMe dataset. The primary rationale for utilizing cortical thickness is that, all else being equal, a region with thicker grey matter is expected to send more endogenous input signals to the rest of the system. This intuition relies on the biologically plausible assumption that a region's capacity to contribute input energy to the network is a function of its total abundance of excitatory neurons—which form most of the inter-regional projections [24]. Thus, cortical thickness serves as a structural proxy for the intrinsic control capacity of each region. This approach is conceptually aligned with recent studies that have applied non-uniform control inputs based on specific biological properties, such as local receptor density, thereby providing a more neurobiologically grounded framework for modeling state transitions [36,37].

Statistical analysis of day-by-day control energy

To assess how the choice of structural connectome influences the estimation of control energy, we mapped a fixed 30-day sequence of functional brain states (SR gradient patterns from the 28andMe dataset; 29 daily transitions) onto four distinct types of structural connectomes. Group A utilized individual, phase-specific connectomes from the 22 participants in the HHS, dynamically updating the structural network to correspond with the menstrual phase to produce 22 control energy time series. Group B employed the group-averaged connectome from the HCP-YA dataset, yielding a single control energy time series. Group C used subject-specific connectomes averaged across all menstrual phases, generating 22 control energy time series. Finally, Group D applied a phase-averaged group connectome, created by averaging the connectomes of all 22 participants within each menstrual phase, resulting in a single control energy time series. For each participant, we utilized a 30-day sequence of brain states (SR gradient patterns) from the 28andMe dataset, resulting in 29 daily state transitions. Control energy was calculated as the minimum energy required to steer the system between these consecutive states.

To quantify the similarity between these trajectories, we computed Pearson correlation coefficients. Within-group similarity (for Groups A and C) was assessed by calculating pairwise correlations among participants' time series to obtain the distribution of within-group correlation values. For comparisons involving single-series groups (Groups B and D), we computed external correlations between their time series and those of multi-series groups. All correlation values were Fisher z-transformed, and two-tailed two-sample z-tests ($\alpha = 0.05$) were conducted to evaluate whether the mean correlation differed significantly between groups. This approach provides a quantitative framework for assessing how control energy dynamics vary depending on the underlying structural connectome, accounting for both within-group similarity and cross-group correspondence.

We compared the variation in control energy between two hormonal conditions: a naturally cycling (drug-free) condition, in which hormones fluctuate endogenously across the menstrual cycle, and a hormonally suppressed condition, in which OC use prevents

endogenous hormonal cycling. Control energy was computed as the minimum energy required to achieve day-by-day brain state transitions across a 30-day sequence of brain states defined by daily SR gradient patterns from the 28andMe dataset. Specifically, to evaluate how much variability each modeling approach of the natural cycle exhibits compared to an OC baseline, we compared the distribution of control energy during the 23 days of oral contraceptive use (drug condition) against six distinct cases from the drug-free period. For the drug-free condition, we employed structural connectomes defined in Groups A, C, and D, and for each connectome type, we applied either a uniform full control set (homogeneous)—assuming equal control input across all regions—or a cortical-thickness-weighted control set (heterogeneous), which assigned control weights based on regional cortical thickness. For the drug condition, menstrual phases were not defined due to hormonal suppression; therefore, we used the Group C connectome approach with the uniform full control set to establish a fixed baseline. To quantify the variability of each drug-free model relative to this baseline, we calculated the 95% reference range ($\text{mean} \pm 1.96 \times \text{standard deviation (SD)}$) of the drug condition's control energy and identified specific energy peaks in the drug-free trajectories that exceeded this range.

Analysis 2: Phase-specific cognitive state transitions, estimated based on HHS structural connectomes

Cognitive maps as brain states in NCT

To define the spatial representations of various cognitive states, we utilized Neurosynth, a brain-mapping framework that integrates text-mining and meta-analysis to generate probabilistic mappings between psychological concepts and regional neural activation [25]. It is important to clarify that these cognitive states are static, spatial activation templates derived from thousands of independent neuroimaging studies.

In this study, we leveraged 123 cognitive activation maps corresponding to diverse cognitive terms selected from the Cognitive Atlas [38], following the specific term list implemented by Luppi et al. (Supplementary Table S1) [24]. Using the NiMARE environment and the Neurosynth database, we performed large-scale meta-analyses to derive these spatial representations [39]. Specifically, multilevel kernel density chi-square contrasts were employed to identify the likelihood of activation associated with each cognitive term. The resulting reverse-inference z-score maps—corrected for multiple comparisons via False Discovery Rate (FDR) correction—provided a probabilistic spatial measure linking regional brain activity to psychological processes. These z-scores represent spatial likelihoods, independent of the temporal domain. To align these whole-brain voxel-wise maps with our anatomical network model, we projected them onto the Schaefer 100-parcel cortical atlas. Specifically, the spatial z-scores of all voxels falling within the precise anatomical boundaries of a given parcel were averaged. By spatially aggregating these voxel-wise scores, we generated static 100-dimensional vectors (which corresponded to Schaefer 100-region cortical atlas) that capture the distinct spatial activation signatures for each cognitive domain. These vectors served as the predefined coordinate points within the state space for estimating phase-specific transition energies using the HHS connectomes.

Statistical analysis of cognitive state transitions

For each of the 123 predefined cognitive spatial representations, we calculated two distinct,

directionally specific transition costs based on pairwise state transitions. Specifically, the initial state and target state for the NCT were defined using the meta-analytic z-score vectors, and the control energy was computed for all possible pairwise state combinations. Inbound transition energy for a given cognitive state was defined as the average control energy required to transition into that target state from all other cognitive states. Conversely, outbound transition energy for a given state was defined as the average control energy required to transition from that specific state into all other cognitive states. This all-to-all state transition approach provides a measure of the global energetic barrier to enter or exit a specific cognitive configuration relative to the broader cognitive landscape.

To investigate the explicit structural constraints imposed by hormonal fluctuations, these pairwise state transition energies were computed separately onto the biologically individualized, phase-specific connectomes of the 22 HHS participants. Rather than utilizing the longitudinal daily functional states from the single-subject 28andMe dataset (as in Analysis 1), this analysis used 123 static meta-analytic spatial maps as predefined target states to evaluate phase-specific structural transition costs. For every participant, the structural connectome was instantiated twice: once using their structural connectome acquired during the early follicular phase (defined here using the menses scan) and once using their connectome from the luteal phase (using the mid-luteal scan). For each of the 123 cognitive domains, we generated paired estimates of mean inbound and outbound control energies constrained by the distinct anatomical wiring of each menstrual phase.

To investigate phase-dependent modulation of these cognitive transition metrics, we performed repeated-measures analysis of variance (rm-ANOVA). Prior to conducting the rm-ANOVA, the assumption of normality for the control energy data was assessed and confirmed via the Shapiro-Wilk test. The alpha level for all omnibus tests was set to $\alpha = 0.05$. In this model, the menstrual phase (follicular and luteal) served as the within-subject factor, while the inbound and outbound energy metrics for the 123 cognitive states served as the dependent variables. Across the 123 cognitive states, the resulting p -values were adjusted for multiple comparisons using the FDR controlled via the Benjamini-Hochberg procedure. To further characterize patterns of phase-dependent energy reallocation, K-means clustering was applied to the cross-phase Energy Delta (defined as follicular mean minus luteal mean) for both inbound and outbound trajectories to identify cognitive groupings exhibiting coherent, phase-dominant stability profiles. To determine the optimal number of clusters for this analysis, we computed the Silhouette coefficient and applied the elbow method on the within-cluster sum of squares. All statistical analyses were implemented in Python using the scipy and statsmodels libraries [40,41].

Results

Analysis 1: Daily control energy dynamics across hormonal conditions

To investigate the impact of endogenous hormonal fluctuations on brain state transitions, we assessed the day-by-day variations in total control energy throughout a complete 30-day natural menstrual cycle. To isolate the associated energetic costs, the 30-day natural cycle trajectories were directly compared against a hormonally suppressed baseline, defined by the 95% reference range derived from the 23-day active OC period. Because mixed linear model

regression indicated that regional cortical thickness differed between the natural cycle and OC conditions (Supplementary Table S2), and to ensure our findings were robust across different structural assumptions, six distinct control energy trajectories were computed for the natural cycle. These were generated by crossing three structural connectome types derived from the HHS dataset (Group A, C and D) with two control set configurations (uniform vs. cortical-thickness-weighted).

As illustrated in Fig. 1, the natural menstrual cycle exhibited markedly higher day-to-day variability in control energy compared to the OC period (see Supplementary Fig. S1 for the OC trajectory). Across the natural cycle, we identified six distinct time points where control energy requirements markedly peaked, surpassing the 95% reference range of the OC baseline: Days 3–4, Day 8, Day 14, Days 17–20, Days 22–23, and Day 25. These peaks temporally coincided with phases of shifting hormonal concentrations, whereas the OC condition maintained a stabilized transition profile without such prominent fluctuations.

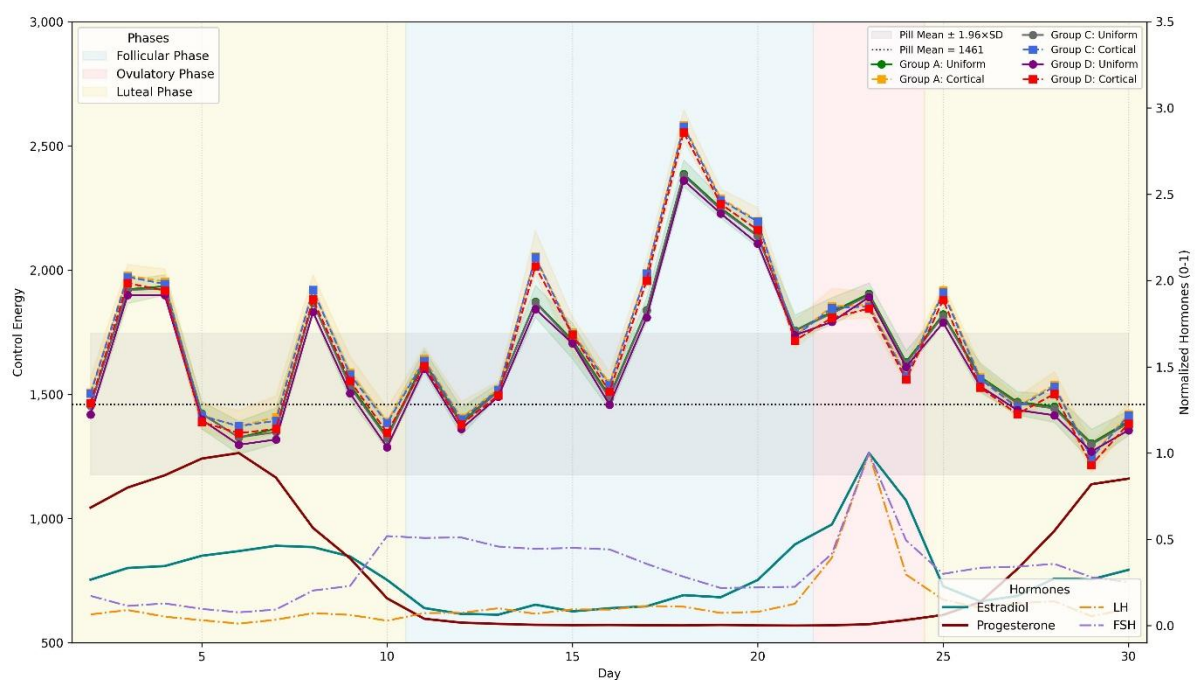


Figure 1. Dynamics of brain state transition energy and hormones across the menstrual cycle. This figure illustrates the integrated dynamics of endogenous ovarian hormones and the energetic costs of brain state transitions across a complete 30-day menstrual cycle. The left y-axis quantifies the total control energy required for day-by-day transitions between functional brain states, derived from the 28andMe SR gradient. These trajectories are modeled using three distinct connectome configurations (Group A, individual phase-specific; Group C, individual subject-averaged; Group D, phase-averaged group connectomes). Within each group, solid lines denote a uniform control strategy, while dashed lines represent a cortical-thickness-weighted control strategy. The shaded gray horizontal band indicates the 95% reference range of control energy during the 23-day active OC period, which serves as a stable, hormonally suppressed baseline for comparison. Background colored spans delineate the major menstrual phases. Overlaid on the right y-axis are the normalized daily concentrations of estradiol, progesterone, LH, and FSH, facilitating a direct visual

comparison between endocrine surges and neural energetic demands.

Having established these hormone-driven energy dynamics, we next sought to evaluate how the choice of structural connectome configuration influenced the estimated control energy trajectories, thereby validating our individualized modeling approach. We compared the alignment between individualized models and group-level templates using Fisher z-transformed Pearson correlation coefficients. As illustrated in Fig. 2, trajectories utilizing subject-specific connectomes (Group A: phase-specific connectomes; Group C: phase-averaged connectomes) exhibited robust within-group correlation distributions. Conversely, the inter-group comparison between Group B (HCP-based group average) and the individualized trajectories of Group A yielded a relatively low mean z-transformed correlation.

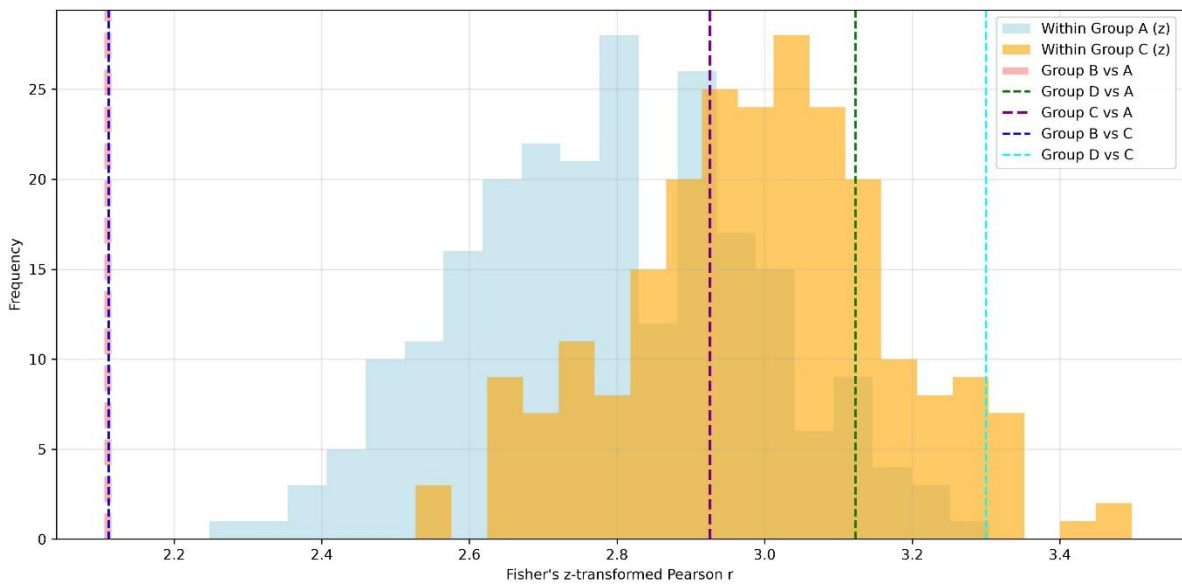


Figure 2. Distribution of within-group and inter-group correlations for control energy trajectories. This figure illustrates the alignment and consistency of control energy dynamics across four connectome groups (Group A: individual, phase-specific connectomes; Group B: HCP-based group-averaged template; Group C: individual subject-averaged connectomes; Group D: phase-averaged group connectomes). Histograms represent the frequency distributions of pairwise within-group Fisher z-transformed correlation coefficients for Group A and Group C, computed across 22 subjects. Vertical dashed lines indicate the mean inter-group correlation values. All coefficients were derived from 29-element control energy vectors under consistent SR gradient transition states.

To determine whether the observed variations in control energy trajectories were statistically significant, we performed two-sample z-tests on the Fisher z-transformed coefficients. This analysis confirmed that control energy patterns derived from the HCP-based template (Group B) differed significantly from those utilizing biologically individualized connectomes, showing marked statistical departure from both Group A ($p = 0.036$) and Group C ($p = 0.007$)

(Fig. 3). Based on these results, we inferred that population-level structural frameworks do not statistically reproduce the energy dynamics observed in models based on individual biological specificities.

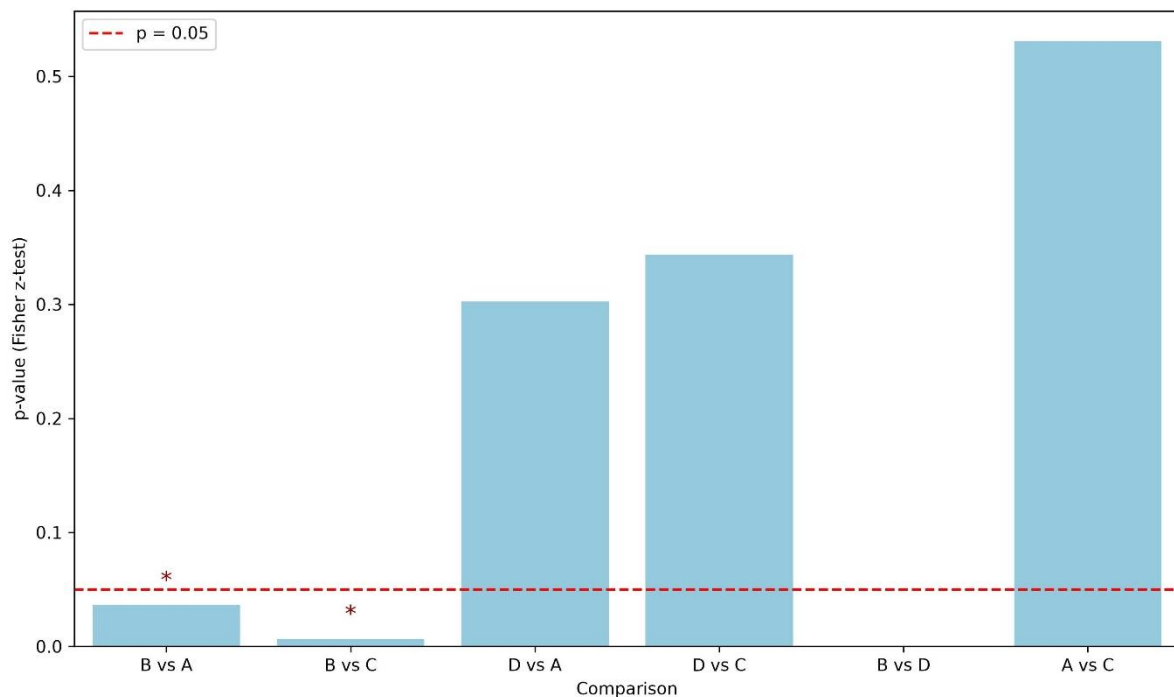


Figure 3. Statistical comparison of group-level control energy correlations. This figure presents a statistical evaluation of whether control energy transition patterns differ significantly across various connectome configurations (Group A: individual, phase-specific connectomes; Group B: HCP-based group-averaged template; Group C: individual subject-averaged connectomes; Group D: phase-averaged group connectomes). Each bar represents the p -value, derived from a two-sample Fisher z-test comparing control energy trajectories between group pairs. The red dashed line indicates the standard alpha threshold for statistical significance ($p = 0.05$). Statistically significant differences ($p < 0.05$) are denoted by an asterisk (*).

Analysis 2: Phase-specific cognitive state transitions

Building upon the finding that endogenous hormonal fluctuations modulate global control energy, we next sought to quantify phase-dependent energetic demands for specific cognitive domains. Inbound and outbound transition energies were calculated across 123 distinct cognitive states for the follicular and luteal phases within the natural cycle using the individual, phase-specific connectomes ($n = 22$) (Supplementary Fig. S2).

Rm-ANOVA revealed nominal main effects of phase (using an uncorrected threshold of $\alpha = 0.05$) on inbound energy for several executive and linguistic states, including response inhibition ($F = 5.51$, $p = 0.008$), language comprehension ($F = 5.43$, $p = 0.008$), and focus ($F = 5.42$, $p = 0.008$) (Supplementary Table S3). For outbound energy, nominal phase-dependent effects were observed in perceptual states, with utility ($F = 4.91$, $p = 0.012$) and face

recognition ($F = 4.84, p = 0.013$) showing the strongest effects. However, after applying the FDR correction for multiple comparisons across all 123 states, no single cognitive state reached the threshold of statistical significance (FDR-adjusted $p > 0.05$; lowest adjusted $p = 0.266$).

Although individual states did not survive FDR correction, to explore broader network-level patterns of energy reallocation on an exploratory basis, K-means clustering was applied to the Energy Delta of the 37 nominally significant states for both inbound and outbound trajectories (Fig. 4). Guided by the optimal Silhouette score, this analysis identified three distinct functional groupings. Cluster 1 (e.g., thought, effort, response inhibition) was characterized by either higher entry costs during the luteal phase (negative Inbound Delta) or minimal inter-phase variance. In contrast, Cluster 2 (e.g., action, selective attention, response selection) exhibited higher entry costs during the follicular phase (positive Inbound Delta) coupled with higher exit costs during the luteal phase (negative Outbound Delta). Finally, Cluster 3 (e.g., face recognition, object recognition, semantic memory) displayed the inverse profile, reflecting lower entry costs (negative Inbound Delta) and higher exit costs (positive Outbound Delta) during the follicular phase.

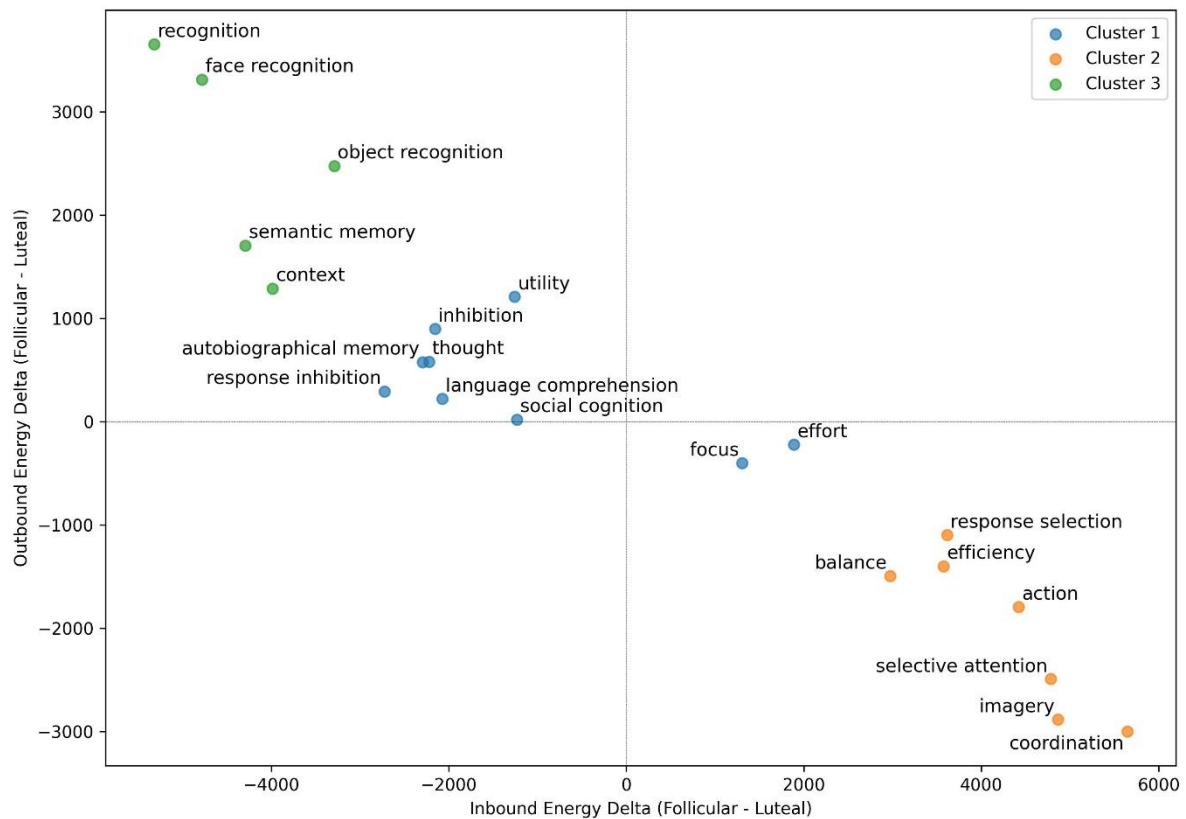


Figure 4. Clustering of significant cognitive states based on energy differentials. This figure illustrates the distribution of 37 cognitive states that exhibited nominal significance ($p < 0.05$) in inbound or outbound energy levels. The axes represent the Energy Delta, calculated as the follicular mean minus the luteal mean. States are grouped into three distinct functional clusters using the K-means algorithm (Cluster 1, higher luteal entry costs or minimal variance; Cluster 2, higher follicular entry and luteal exit costs; Cluster 3, inverse

profile with higher follicular exit costs).

Discussion

Our findings demonstrate that dynamic sex hormone changes during the menstrual cycle actively steer macroscale brain dynamics. By leveraging network control theory, we show that the endocrine environment systematically modulates the control energy landscape—spanning daily shifts in information-processing configurations (measured via SR gradient) to phase-specific transition energies across diverse cognition-related activation maps. Specifically, we observed that the natural cycle is characterized by substantial fluctuations in control energy, with peaks temporally aligned with major hormonal transitions—a pattern that was flattened under OC-induced hormonal suppression. This rhythmic volatility stands in stark contrast to the uniform, stabilized network states induced by OCs, suggesting that endogenous hormonal cycling is associated with elevated control energy demands for maintaining daily functional brain states. Importantly, this energetic cost perspective mechanistically contextualizes prior resting-state fMRI findings that have reported widespread fluctuations in intrinsic connectivity and network modularity across menstrual phases [9,11]. Furthermore, our cognitive state transition analyses indicate that the menstrual cycle is accompanied by a systematic reconfiguration of neural resource allocation across distinct cognitive domains. A summary of these multiscale dynamics is illustrated in Fig. 5.

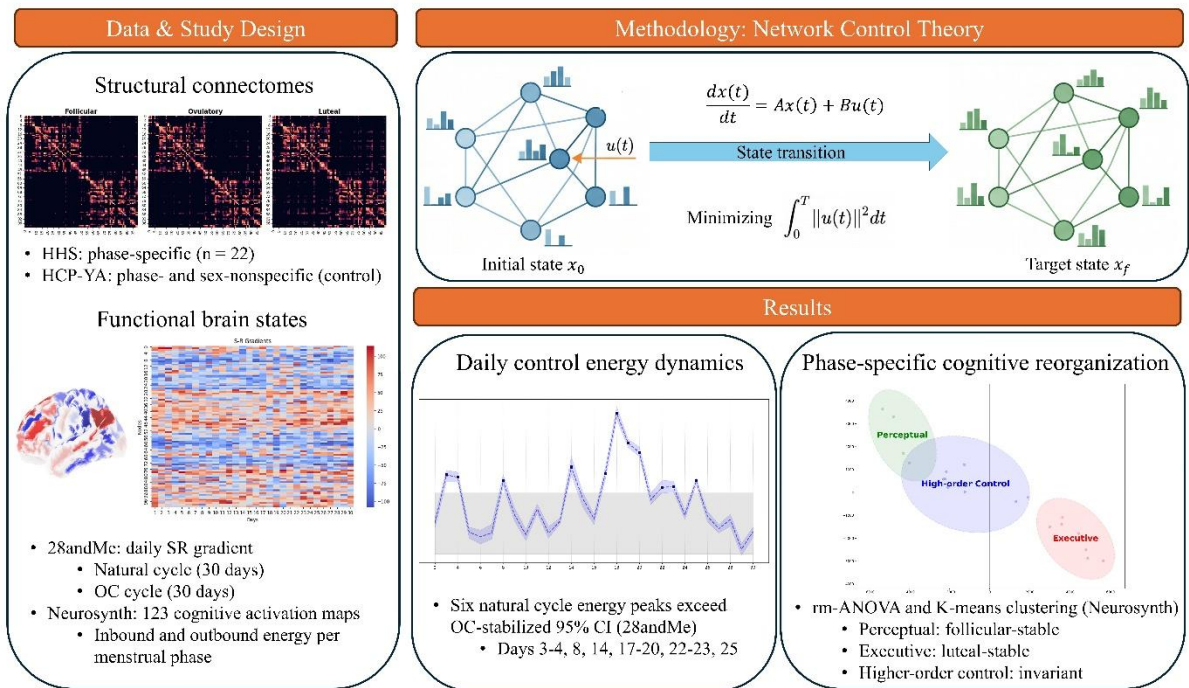


Figure 5. Overview of the study design, methodology, and main findings.

Our findings further demonstrate that structural connectome fidelity is a critical variable in control energy dynamics. The high internal consistency observed in individualized frameworks (Groups A and C) indicates a strong alignment between individual structural

architecture and modeled functional transitions. While underlying anatomical wiring imposes fundamental constraints on functional dynamics, it is important to note that this relationship is interactive; functional engagement and learning can also drive structural remodeling over time. Nevertheless, within the timescale of this study, an individual's unique structural fingerprint provided the most reliable scaffold for estimating energy requirements amidst physiological fluctuations. The significant divergence of the HCP-based template (Group B) from individualized models highlights a limitation of population-level averages in capturing the nuanced energetic shifts inherent in dynamic, individualized biological processes.

A key methodological question in NCT is the configuration of the control set. While recent benchmarks suggest that a homogeneous full control set—where all nodes possess equal control authority—serves as a useful baseline [27], this assumption often lacks biological realism. In the present study, we observed divergent trajectories in control energy when comparing homogeneous sets to heterogeneous sets weighted by cortical thickness. Following the framework established by Luppi et al. [24], we utilized cortical thickness to assign differential regional control weights. We acknowledge that cortical thickness is a complex, multifactorial metric rather than a direct one-to-one measure of neuronal density; nevertheless, utilizing it as a macroscale heuristic for regional control capacity provides a more biologically informed weighting than assuming uniform control across the entire cortex [42,43]. The sensitivity of the energy trajectories to these parameters suggests that incorporating regional morphometry is essential for capturing the subtle neuroendocrine modulations of brain dynamics.

The most salient finding of this study is the temporal alignment between hormonal transitions and peaks in control energy. In the natural cycle, we identified six time points at which control energy requirements exceeded the 95% reference range of the stabilized OC baseline, each co-occurring with periods of shifting endocrine concentrations. This energetic cost is particularly evident during the transition on Days 3 and 4, which coincides temporally with the markedly elevated negative affect scores originally reported for this participant in the 28andMe dataset characterization: tension (Days 3–5 average: 11.33 vs. 30-day average: 4.13), depression (13.67 vs. 2.20), anger (5.33 vs. 1.12), and anxiety (54.33 vs. 35.68) [44]. Rather than a generalized conclusion, we frame these findings as a proof-of-concept case observation. Because these observations are derived from a single participant, they must be interpreted strictly as descriptive and hypothesis-generating. Nonetheless, they broadly parallel the clinical profile of premenstrual symptoms [44,45]. The co-occurrence of elevated control energy and affective symptom scores in this individual raises an intriguing hypothesis for future clinical research: the increased control energy during symptomatic windows may represent a quantifiable neural cost of maintaining functional stability amidst rapid endocrine reconfiguration [46]. This goes beyond the consensus that hormones alter brain states, proposing a testable mechanistic framework (neural energetic cost) to better understand the cognitive and affective burden experienced by some naturally cycling women.

In particular, the sustained elevation in control energy across Days 17–20 (peaking around Day 18)—which immediately preceded the ovulatory LH surge window (Days 22–24)—provides an intriguing window into the regulatory mechanisms of the hypothalamic-pituitary-gonadal (HPG) axis. The HPG axis typically operates under negative feedback, but the ovulatory phase involves a switch to positive feedback, in which rising estradiol triggers an LH surge rather than suppressing gonadotropins [47]. This transition involves complex

processes, including increased GnRH receptor sensitivity in the pituitary and the suppression of nonsteroidal ovarian products like gonadotropin surge-attenuating factors [48,49]. The temporal coincidence of the control energy peak with the pre-ovulatory window raises the possibility that this shift in endocrine regulation is accompanied by a substantial reorganization of neural control demands. That the peak precedes the LH surge is consistent with the hypothesis that the brain undergoes a high-energy re-tuning prior to the positive feedback loop taking hold. The absence of comparable peaks in the OC condition, in which feedback transitions and gonadotropin surges are pharmacologically suppressed, is consistent with this interpretation.

This study presents preliminary evidence—derived from projecting meta-analytic cognitive states onto HHS phase-specific connectomes ($n = 22$)—that hormonal fluctuations across the menstrual cycle may redistribute the brain's transition energy dynamics to create phase-specific functional networks. Within the network control framework, a cognitive state is functionally stable when its entry barrier (inbound energy) is low, and its exit barrier (outbound energy) is high. Based on this framework, the analysis identified distinct phase-dominant architectures across different cognitive domains. Sensory and perceptual states demonstrated optimal functional stability during the follicular phase, a pattern that theoretically aligns with existing literature suggesting elevated estrogen facilitates sensory-driven processing and sustained information retention [50-53]. In contrast, executive function and motor coordination showed peak stability during the luteal phase, which may reflect progesterone's stabilizing effect on cortical networks and GABAergic inhibition [7]. During the follicular phase, however, these executive states became more transient, which may instead promote rapid state-switching and cognitive flexibility [54]. Meanwhile, high-level cognitive control states remained relatively unchanged across the cycle, suggesting that baseline cognitive stability is actively shielded from major hormonal shifts [55,56]. Crucially, it must be noted that while these patterns emerged at the nominal level, they did not survive FDR correction. Given this statistical limitation and the integration of meta-analytic maps rather than direct behavioral assessments, specific neurobiological mechanisms, such as GABAergic or dopaminergic modulations, remain highly speculative. Therefore, these interpretations should be viewed as theoretically aligned hypotheses rather than definitive conclusions. It is currently debatable whether these theoretical energy shifts translate to measurable behavioral differences. Therefore, robust validation in large, diverse cohorts paired with objective cognitive assessments is strictly necessary before drawing any clinical or generalizable conclusion.

While this study provides a novel theoretical perspective on hormonal cycles and brain dynamics, several critical limitations must be acknowledged. Most notably, the foundational longitudinal functional analyses rely on a single, densely sampled individual (28andMe dataset). It is important to note that this single-subject, dense-sampling design was deliberately chosen following the 'precision functional mapping' paradigm. Traditional cross-sectional or group-averaged studies often obscure intra-individual, day-to-day temporal dynamics due to profound inter-subject variability in cycle length, hormone baselines, and individual brain architecture. By adopting this precision approach, we were able to track energetic shifts within-person with the high temporal resolution required to capture daily endocrine fluctuations. Nevertheless, given the significant inter-individual variability in menstrual experiences and affective symptomology, extrapolating these single-subject temporal trajectories to the broader female population is not advisable without further

validation. Furthermore, our analytic pipeline integrates data from three non-overlapping populations (the HHS phase-specific connectomes, the 28andMe functional states, and the Neurosynth meta-analytic maps). Although inter-group consistency was evaluated, residual between-population heterogeneity may still influence the absolute magnitude of the estimated control energy.

Methodologically, the computational models employed rest on specific theoretical assumptions. NCT models the brain as a linear time-invariant dynamical system, making the resulting control energy a theoretical construct rather than a directly measured metabolic cost. Similarly, the SR gradient represents only one of several possible operationalizations of daily functional brain states. Statistically, as noted above, the cognitive interpretations derived from the K-means clustering rest on nominal-level signals and must be viewed as preliminary and hypothesis-generating.

Lastly, there are constraints regarding biological mapping and phenotypic outcomes. Our control set assumes that cortical thickness serves as the primary determinant of regional control authority. While a useful macroscale heuristic, this simplification cannot capture the full complexity of excitatory-inhibitory balances, such as progesterone-modulated GABAergic inhibition. Most importantly, our findings lack concurrent objective behavioral or cognitive performance measures. Although we observed temporal co-occurrences between hormonal transitions, affective symptom scores, and control energy peaks, the causal directionality cannot be established. Furthermore, it remains unknown whether increased theoretical control energy manifests as observable behavioral deficits, or whether it reflects compensatory neural efforts required to maintain stable cognitive performance amidst hormonal shifts. Future perturbation studies and larger longitudinal cohorts paired with rigorous cognitive testing are essential to determine whether these theoretical energetic fluctuations translate into measurable behavioral differences.

Future work should pursue replication and extension along several axes. First, larger group-level longitudinal studies, with dense sampling across multiple participants from racially, socioeconomically, and culturally diverse cohorts, are needed to establish whether the phase-specific energetic patterns and cognitive state clusters reported here generalize across individuals. Second, pairing control energy estimation with behavioral assessment would clarify whether phase-dependent energy reallocation is associated with measurable shifts in cognitive flexibility, executive function, or affective processing. Third, comparisons across different hormonal contexts—including distinct oral contraceptive formulations, the peri- and post-menopausal transition, and clinical populations with premenstrual dysphoric disorder or hormonally sensitive mood disorders—would help delineate which features of the energetic landscape are hormone-driven versus endogenous to cycling physiology. Finally, extending the control set parameterization to incorporate inhibitory as well as excitatory regional properties would more faithfully represent the neurobiological substrates of control. By bridging network control theory with clinical observation of hormonal cycles, this line of work offers a novel theoretical foundation to advance our mechanistic understanding of emotional and cognitive regulation in naturally cycling individuals, hormonal contraceptive users, and those experiencing hormonal mood disorders. Ultimately, these NCT-based energetic insights hold the potential to inform future research and clinical applications in women's brain health and precision neuropsychiatry.

Data availability statement

The 28andMe dataset is available at <https://openneuro.org/datasets/ds002674/versions/1.0.6>, and the HHS dataset can be accessed at <https://openneuro.org/datasets/ds005360/versions/1.0.1>. The code used in this study is hosted on GitHub at https://github.com/phs9416/NCT_Menstrual.

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909 **Author contributions**

910 H.S.P. and B.J. conceptualized and supervised the study. H.S.P., H.K., and Y.K. developed the
911 methodology, conducted the formal analysis and investigation, and prepared the figures.
912 H.S.P. and H.K. curated the data, while H.K. provided the software. B.J. acquired funding,
913 provided resources, and administered the project. H.S.P., H.K., and Y.K. wrote the main
914 manuscript text. H.S.P. and B.J. reviewed and edited the text. All authors reviewed the
915 manuscript.

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917 **Competing interests**

918 The authors declare no competing interests.

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