Estradiol shapes resting-state functional connectivity over a complete reproductive cycle

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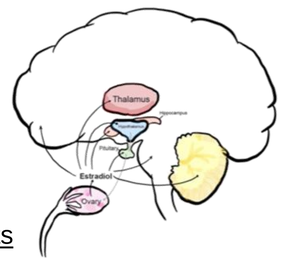
UCSB BRAIN INITIATIVE

INTRODUCTION

- The brain is an endocrine organ
  - Hormonal effects on the central nervous system can be measured across spatial and temporal scales, influencing brain structure and function[1].
  - Across a typical menstrual cycle (~28 days), the average female will experience a 12-fold increase in estrogen and an 800-fold increase in progesterone[2].



- Sex hormones potential source of intra-subject variability in fMRI assessments
  - Recent approaches in neuroscience have moved towards densely sampling individuals to understand sources of intra-subject variability in the stability of functional brain networks over time[3-5].
  - These studies have largely overlooked the effects of sex steroid hormones, which fluctuate within and between individuals[6].
- Current study: How do sex steroid hormones impact resting-state functional connectivity?
  - In this dense-sampling, deep phenotyping case study, **we examined the extent to which endogenous fluctuations in sex steroid hormones across a complete reproductive cycle alter functional connectivity of brain networks at rest.**

METHODS

PARTICIPANT: The participant (author LP) is a right-handed Caucasian female, aged 23 years old at the onset of the study. She is a healthy, regularly and naturally cycling woman, with no history of neuropsychiatric or endocrine disorders.

DATA COLLECTION: LP underwent daily time-locked (±30 min) blood draws and MRI scans for 30 consecutive days. Venous blood sampling took place each morning to evaluate serum concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH), 17β-estradiol (E), and progesterone (P) via liquid chromatography-mass spectrometry, conducted at the Brigham and Women's Research Assay Core.

Behavior Survey — **Virtual Navigation Task** — **Serum Sample** — **s/fMRI**

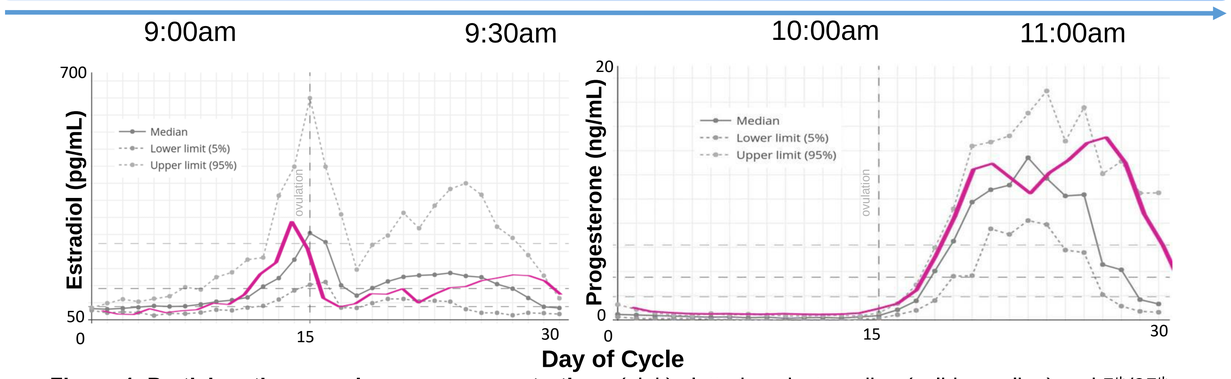


Figure 1. Participant's serum hormone concentrations (pink) plotted against median (solid grey line) and 5th/95th percentiles (dotted grey lines) hormone concentrations based on serum samples from 20 naturally cycling females[2].

MRI PROCESSING: We acquired a daily 10 min. resting-state scan on a 3T Siemens Prisma at the UCSB Brain Imaging Center (T2* multi-band EPI; 72 oblique slices; TR = 720 ms; voxel size = 2 mm^3). Data were realigned/unwarped, registered to a subject-specific anatomical template (created with ANTs), and smoothed (5mm FWHM) in SPM12; in-house Matlab scripts were used for additional preprocessing, including global scaling, detrending, nuisance regression, and temporal filtering using a maximal overlap discrete wavelet transform.

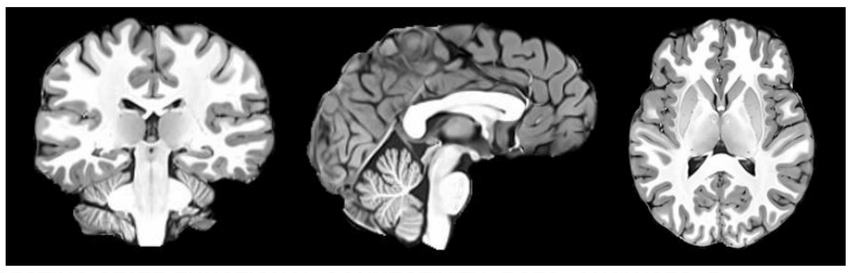
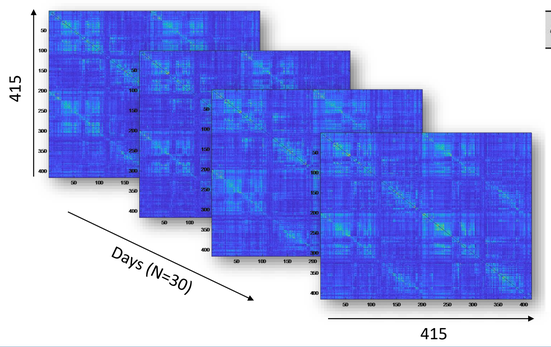
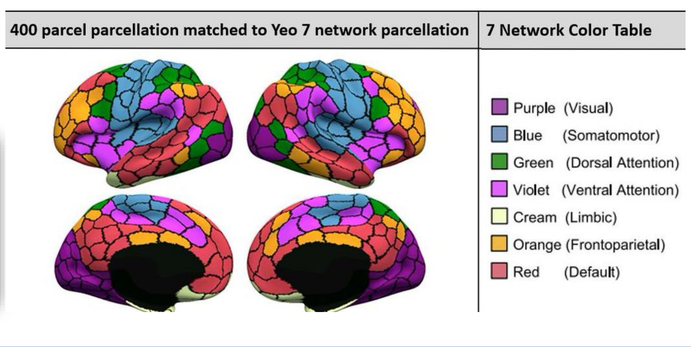


Figure 2. Functional images were registered to a subject-specific template, created by averaging 10 high-resolution T1 MPRAGE structural scans in ANTS.

RESTING-STATE FUNCTIONAL CONNECTIVITY (RSFC) ANALYSES: For each day, we extracted eigen-timeseries from 415 network nodes defined by the Schaefer[7] cortical parcellation and Harvard-Oxford subcortical atlas. Pairwise functional connectivity was estimated via magnitude squared coherence, restricted to low-frequency fluctuations in wavelet scales 3-6 (~0.01 - 0.17 Hz). All association matrices were FDR-thresholded (q<0.05). We used common graph theoretic metrics to characterize functional network topology: **efficiency** (a measure of *within* network integration) and **participation coefficient** (a measure of *between* network integration)[8]. These were estimated for each of the Yeo 7 network parcellations[9] and a subcortical network.





CONCLUSIONS

- Serum concentrations of E and P were within expected ranges[6], and showed the canonical fluctuations across the menstrual cycle, with E peaking in late follicular phase and P concentrations rising dramatically during the mid-luteal phase.
- Time-synchronous analyses: **Increases in estradiol over time are associated with greater functional connectivity across the whole brain.**
- Time-Lagged analyses: **Estradiol drives Default Mode connectivity,** within (efficiency) and between (participation) networks. This pattern was also observed in Dorsal Attention, Frontoparietal, and Limbic networks.
- The brain is an endocrine organ; consideration of the hormonal milieu is necessary to fully understand intrinsic brain dynamics.

References

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RESULTS

Time-Synchronous Analysis: Edgewise Regression

Increases in estradiol over time are associated with **greater functional connectivity** across the **whole brain**

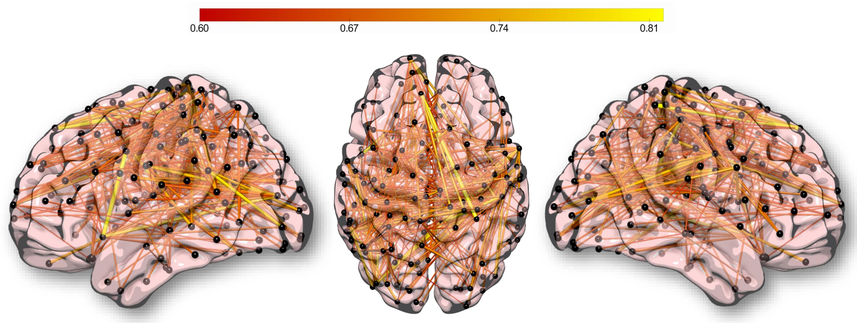


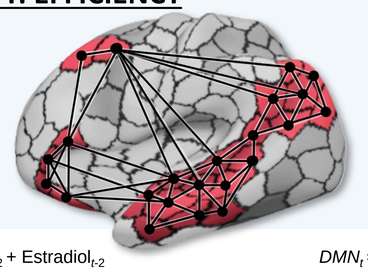
Figure 3. Standardized regression between coherence and estradiol (L, left; M, dorsal; R, right) at each edge. 'Hotter' colors indicate stronger coherence with increasing estradiol concentrations (FDR-corrected, q < 0.05).

Time-Lagged Analysis: Vector Autoregression

In order to more directly capture time-dependent modulation of network connectivity and hormonal states, we specified and estimated simultaneous 2nd-order vector autoregressive models:

$$DMN_t = DMN_{t-1} + Estradiol_{t-1} + DMN_{t-2} + Estradiol_{t-2}$$
$$Estradiol_t = DMN_{t-1} + Estradiol_{t-1} + DMN_{t-2} + Estradiol_{t-2}$$

WITHIN-NETWORK CONNECTIVITY: EFFICIENCY



Estradiol$_t$ = DMN$_{t-1}$ + Estradiol$_{t-1}$ + DMN$_{t-2}$ + Estradiol$_{t-2}$

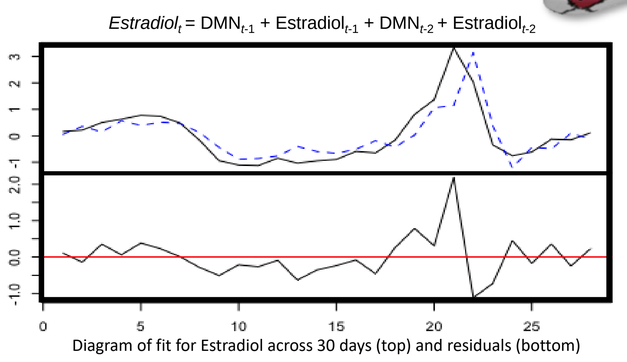


Diagram of fit for Estradiol across 30 days (top) and residuals (bottom)

Term	Est	*SE*	*t*	*p*
DMN$_{t-1}$	-0.19	0.16	-1.13	.369
Estro$_{t-1}$	**1.28**	**0.23**	**5.59**	**<.001**
DMN$_{t-2}$	-0.01	0.15	-0.05	.965
Estro$_{t-2}$	**-0.57**	**0.22**	**-2.56**	**.003**

$F(4,24) = 12.88$, $p < .001$; $R^2 = 0.68$

estradiol ← DMN efficiency ✗

DMN$_t$ = DMN$_{t-1}$ + Estradiol$_{t-1}$ + DMN$_{t-2}$ + Estradiol$_{t-2}$

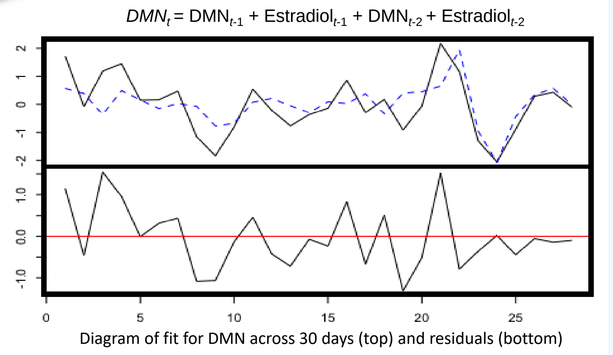


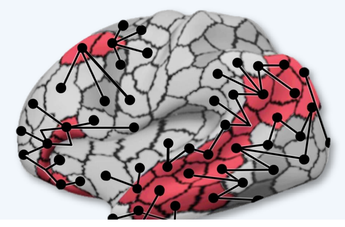
Diagram of fit for DMN across 30 days (top) and residuals (bottom)

Term	Est	*SE*	*t*	*p*
DMN$_{t-1}$	0.21	0.21	0.99	.292
Estro$_{t-1}$	**0.71**	**0.29**	**2.39**	**.002**
DMN$_{t-2}$	-0.23	0.20	-1.15	.275
Estro$_{t-2}$	**-0.64**	**0.29**	**-2.24**	**.003**

$F(4,24) = 5.05$, p=.004; $R^2 = 0.47$

estradiol → DMN efficiency ✓

BETWEEN-NETWORK CONNECTIVITY: PARTICIPATION



Estradiol$_t$ = DMN$_{t-1}$ + Estradiol$_{t-1}$ + DMN$_{t-2}$ + Estradiol$_{t-2}$

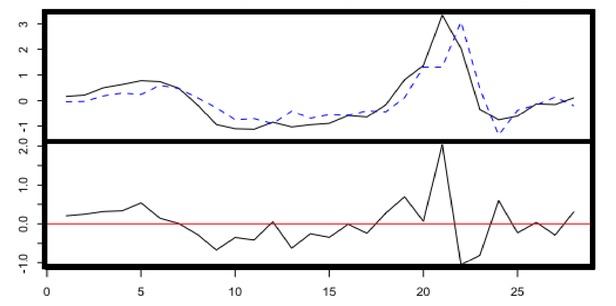


Diagram of fit for Estradiol across 30 days (top) and residuals (bottom)

Term	Est	*SE*	*t*	*p*
DMN$_{t-1}$	0.08	0.12	0.65	.690
Estro$_{t-1}$	**1.13**	**0.18**	**6.42**	**<.001**
DMN$_{t-2}$	-0.08	0.12	-0.65	.688
Estro$_{t-2}$	**-0.51**	**0.18**	**-2.87**	**.007**

$F(4,24) = 12.25$, $p < .001$; $R^2 = 0.671$

estradiol ← DMN participation ✗

DMN$_t$ = DMN$_{t-1}$ + Estradiol$_{t-1}$ + DMN$_{t-2}$ + Estradiol$_{t-2}$

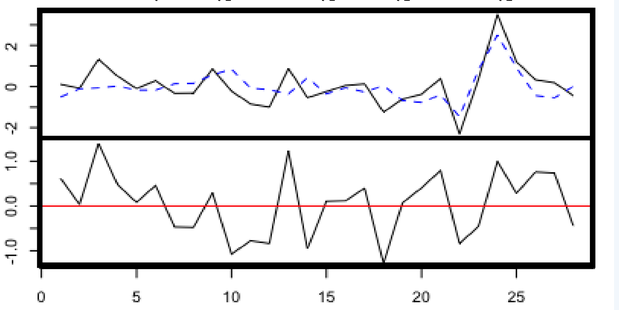


Diagram of fit for DMN across 30 days (top) and residuals (bottom)

Term	Est	*SE*	*t*	*p*
DMN$_{t-1}$	0.19	0.15	1.24	.332
Estro$_{t-1}$	**-.85**	**0.22**	**-3.92**	**<.001**
DMN$_{t-2}$	-.14	0.15	-.95	.464
Estro$_{t-2}$	**.90**	**0.22**	**4.15**	**<.001**

$F(4,24) = 5.82$, p=.002; $R^2 = 0.492$

estradiol → DMN participation ✓

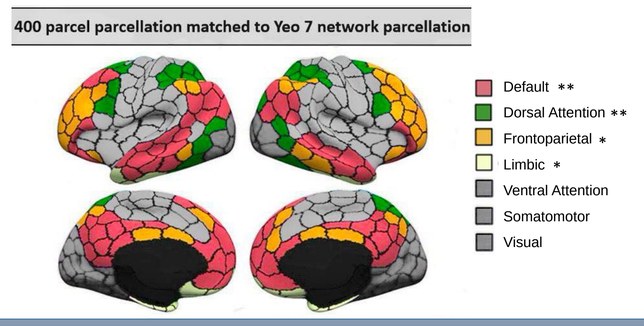


Figure 3. Applying these methods across all networks revealed that **estradiol drives greater functional coherence within estrogen-receptor (ER) rich networks (frontoparietal, dorsal attention, limbic) with little to no influence in ER-poor networks (e.g. Visual).** '*' denotes network model significance after 1,000 iterations of nonparametric permutation testing: *p<.01 *p<.05