Functional reorganization of brain networks across the human menstrual cycle

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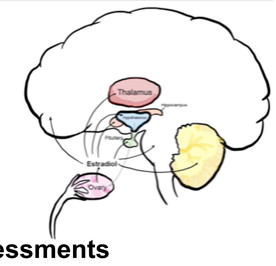
UCSB BRAIN INITIATIVE

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 are a 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 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: The participant underwent time-locked (±30 min) blood draws and MRI scans for 30 consecutive days (*see daily experimental protocol below*). 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.

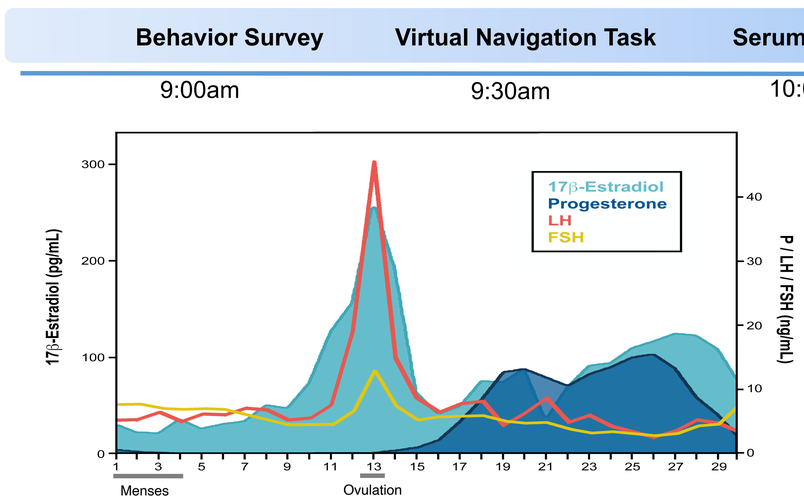


Figure 1. Participant's hormone concentrations plotted by day of cycle; E, P, LH, and FSH levels fell within standard ranges[2].

MRI PROCESSING: We acquired daily 10 min. resting-state scans on a 3T Siemens Prisma at the UCSB Brain Imaging Center (T2* multi-band EPI; 72 oblique slices; TR = 720 ms; voxel size = $2mm^3$). Data were realigned/unwarped, registered to a subject-specific anatomical template (created with ANTs), and smoothed (4mm 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.

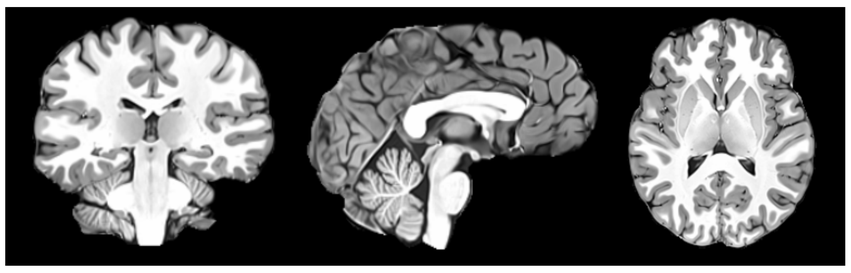
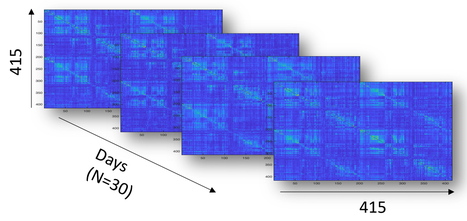
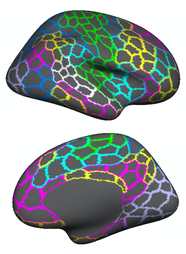


Figure 2. Functional images were registered to a subject-specific template, created by averaging 30 high-resolution T1 MPRAGE structural scans in ANTS.

FUNCTIONAL CONNECTIVITY ESTIMATION: 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).



STATISTICAL ANALYSES:
First, we assessed time-synchronous variation in functional connectivity associated with estradiol and progesterone through a standardized regression analysis. Then, we used vector autoregressive models (VAR) to capture linear dependencies between hormones and network connectivity directed in time. We used common graph theoretic metrics to characterize functional network topology; here we focus on **global efficiency** (a measure of *within* network integration). These were estimated for each of the Yeo network parcellations[7,9] and a subcortical network. Results are empirically thresholded via 10,000 iterations of nonparametric permutation testing (p < .001)

Network parcellation	Network color table
	Default Mode Frontal Control Dorsal Attn. Visual Temporal Parietal Salience Ventral Attn. Limbic SomatoMotor

CONCLUSIONS

- Serum hormone concentrations confirmed the expected rhythmic changes of a typical menstrual cycle, with estradiol and progesterone peaking in late follicular (E) and late luteal (P) phases.
- **Time-synchronous analyses**: **Estradiol and progesterone demonstrate positive and negative relationships with whole-brain functional connectivity, respectively.**
- **Time-lagged analyses: Estradiol facilitates tighter coherence within functional brain networks densely populated with estrogen receptors such as the dorsal attention, default mode, and to a lesser extent, frontal control network.**
- Importantly, these **results were replicated** in a controlled, intra-individual follow-up study one year later.
- The brain is an endocrine organ; consideration of the hormonal milieu is necessary to fully understand intrinsic brain dynamics.

References
1. Galea *et al. Neurosci Biobehav Rev. 76*, 363-379 (2017) 2. Stricker *et al. Clin Chem Lab Med. 44*, 883-887 (2006) 3. Finn *et al. Nat Neurosci. 18(11),* 1664 (2015) 4. Poldrack *et al. Nat Commun. 6*, 8885 (2015) 5. Gratton *et al. Neuron. 98(2),* 439-452 (2018) 6. Fehring et al. *J Obstet Gynecol Neonatal Nurs. 35(3),* 376-384 (2006) 5. 7. Schaefer *et al. Cereb. Cortex.* 1-20 (2017*).* 8. Bullmore et al. *Annu. Rev. Clin. Psychol. 7,* 113-140 (2011) 9. Yeo et al. *J. Neurophysiol. 106(3),* 1125 (2011)

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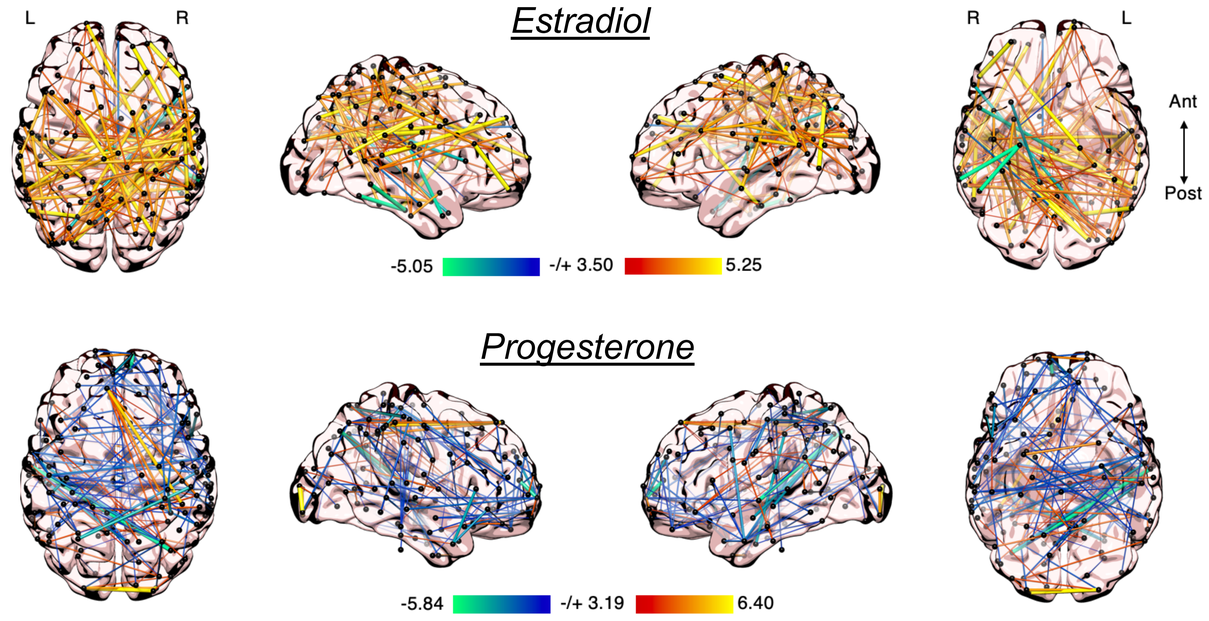
RESULTS

Time-Synchronous Analysis: Edgewise Regression

Standardized regression between coherence and sex hormones at each edge.
'Hotter' colors indicate stronger coherence with increasing sex hormone concentrations; cool colors indicate the reverse.



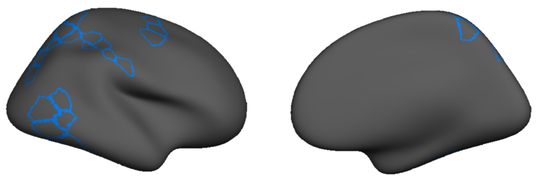
Increases in estradiol over a menstrual cycle are associated with **greater functional connectivity** across the **whole brain,** while **rises in progesterone** are largely associated with **decreases in whole-brain functional connectivity.**

Time-Lagged Analysis: Vector Autoregression

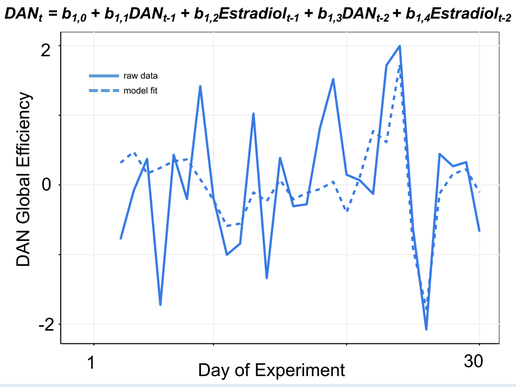
To capture time-dependent modulation of network efficiency metrics and estradiol, we specified and estimated simultaneous 2nd-order vector autoregressive models:

$$Brain_t = b_{1,0} + b_{1,1}Brain_{t-1} + b_{1,2}Estradiol_{t-1} + b_{1,3}Brain_{t-2} + b_{1,4}Estradiol_{t-2} + \epsilon_{1,t}$$
$$Estradiol_t = b_{2,0} + b_{2,1}Brain_{t-1} + b_{2,2}Estradiol_{t-1} + b_{2,3}Brain_{t-2} + b_{2,4}Estradiol_{t-2} + \epsilon_{2,t}$$

Dorsal Attention Network



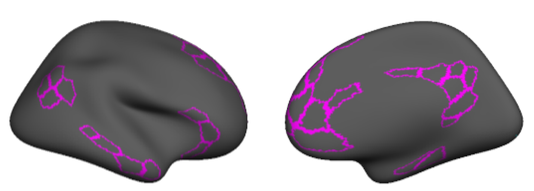
$$DAN_t = b_{1,0} + b_{1,1}DAN_{t-1} + b_{1,2}Estradiol_{t-1} + b_{1,3}DAN_{t-2} + b_{1,4}Estradiol_{t-2} + \epsilon_{1,t}$$



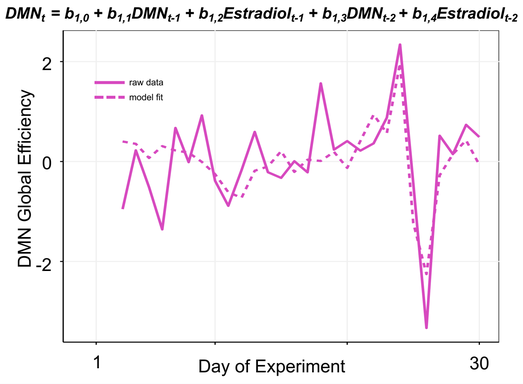
Term	Est	*SE*	*t*	*p*
Constant	0.01	0.6	0.08	.783
DAN_{t-1}	-0.11	0.18	-0.60	.562
$Estro_{t-1}$	**0.84**	**0.25**	**3.35**	**.002**
DAN_{t-2}	-0.10	0.18	-0.58	.571
$Estro_{t-2}$	**-0.67**	**0.16**	**-2.57**	**.017**

R^2 = 0.37 (p = .002); *RMSE* = 0.77 (p = .023)

Default Mode Network



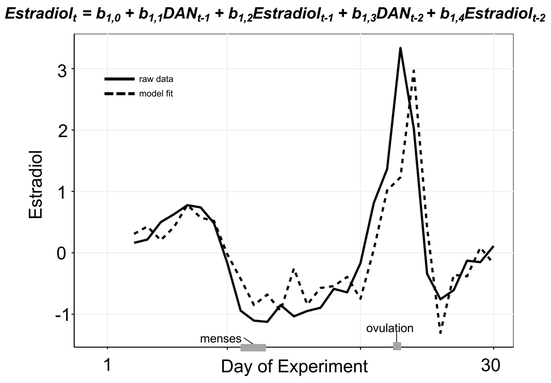
$$DMN_t = b_{1,0} + b_{1,1}DMN_{t-1} + b_{1,2}Estradiol_{t-1} + b_{1,3}DMN_{t-2} + b_{1,4}Estradiol_{t-2} + \epsilon_{1,t}$$



Term	Est	*SE*	*t*	*p*
Constant	0.04	0.15	0.28	.279
DMN_{t-1}	-0.04	0.16	-0.27	.764
$Estro_{t-1}$	**0.98**	**0.23**	**3.37**	**.0003**
DMN_{t-2}	-0.02	0.16	-0.11	.907
$Estro_{t-2}$	**-0.93**	**0.23**	**-4.00**	**.002**

R^2 = 0.50 (p = .003); *RMSE* = 0.70 (p = .022)

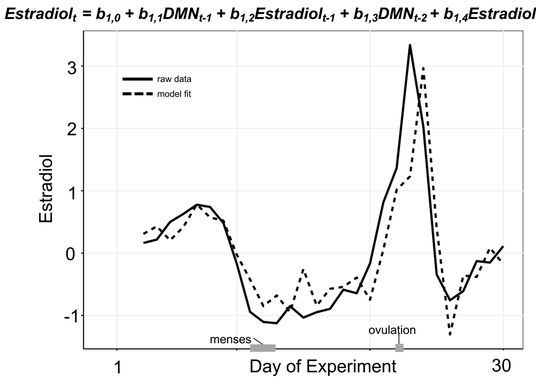
$$Estradiol_t = b_{1,0} + b_{1,1}DAN_{t-1} + b_{1,2}Estradiol_{t-1} + b_{1,3}DAN_{t-2} + b_{1,4}Estradiol_{t-2} + \epsilon_{1,t}$$



Term	Est	*SE*	*t*	*p*
Constant	0.01	0.12	0.06	.808
DAN_{t-1}	-0.17	0.13	-1.29	.207
$Estro_{t-1}$	**1.17**	**0.19**	**6.30**	**< .0001**
DAN_{t-2}	-0.02	0.13	0.24	.806
$Estro_{t-2}$	**-0.48**	**0.18**	**-2.49**	**.011**

R^2 = 0.68 (p < .0001); *RMSE* = 0.77 (p = .0004)

$$Estradiol_t = b_{1,0} + b_{1,1}DMN_{t-1} + b_{1,2}Estradiol_{t-1} + b_{1,3}DMN_{t-2} + b_{1,4}Estradiol_{t-2} + \epsilon_{1,t}$$



Term	Est	*SE*	*t*	*p*
Constant	0.01	0.12	0.09	.729
DMN_{t-1}	-0.12	0.13	-0.95	.339
$Estro_{t-1}$	**1.15**	**0.19**	**6.15**	**< .0001**
DMN_{t-2}	-0.01	0.13	-0.08	.930
$Estro_{t-2}$	**-0.48**	**0.19**	**-2.50**	**.012**

R^2 = 0.67 (p < .0001); *RMSE* = 0.58 (p = .0004)

Intrinsic network dynamics may be driven by recent states of estradiol, particularly with respect to within-network connectivity of the dorsal attention and default mode networks.