INTRODUCTION

• The cerebellum exhibits rich expression of sex steroid hormones and receptors.
• 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.
• Previous work demonstrates that estradiol shapes functional connectivity of the cerebral cortex across the cycle.
• Current study: How do sex steroid hormones impact resting-state functional connectivity of the cerebellum?
• Utilized the 28andMe dataset to examine the extent to which endogenous fluctuations in estradiol and progesterone across a complete menstrual cycle alter functional connectivity of cerebellar networks at rest.

METHODS

PARTICIPANT: The participant 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 neuroendocrine or endocrine disorders.

DATA COLLECTION: The participant underwent daily time-locked (30 min) blood draws and MRI scans for 30 consecutive days. Venous blood sampling took place each evening 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.

MRI PROCESSING: We acquired a daily 10 min. resting-state scan on a 3T Siemens Prisma at the UCSC Brain Imaging Center (128 multi-band EPI, 72 oblique slices; TR = 720 ms; voxel size = 2 mm3). Data were realigned/unwarped, registered to a subject-specific anatomical template (created with ANTs), and smoothed (4 mm 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. Signal from the adjacent left/right cerebral cortex within 7 mm of the cerebellum was regressed out.

RESTING-STATE FUNCTIONAL CONNECTIVITY (RSFC) ANALYSES:

For each day, eigen-timeseries from 99 clusters defined by the Ren et al atlas were extracted and assigned to 7 functional networks identified by Buckner et al4. Edgewise 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). Common graph theory metrics were employed to characterize functional network topology. Efficiency (a measure of within network integration) and participation coefficient (a measure of between network integration)6. Spearman’s correlation was used to address associations between hormones and network topologies, while vector autoregressive models evaluated time-lagged effects.

RESULTS

Time-Synchronous Analysis: Edgewise Regression

Increases in progesterone and estradiol across the cycle are associated with diminished cerebellar functional connectivity

Figure 2. Edgewise regression between coherence and hormones. ‘Cooler’ colors indicate decreasing coherence with increasing hormone concentrations (FDR-corrected, q < .05).

Time-Synchronous Analysis: Correlation

Increases in estradiol across the cycle are correlated with decreases in global efficiency

Figure 3. Time-synchronous associations between network efficiency and estradiol. Spearman’s correlation between global efficiency and estradiol (FDR-corrected at q < .05).*** indicates p < .001. SMN and VAN efficiency were greater than three standard deviations from the mean on day 21 of cycle and were removed from the plot. Abbreviations: DAN, Dorsal Attention Network; SMN, Somato-Motor Network; VAN, Ventral Attention Network.

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:

BETWEEN-NETWORK CONNECTIVITY

• Estradiol did not predict between-network connectivity.
• Cerebellar DMN and SMN exhibited significant autoregressive effects of connectivity at lag 1 but lacked significant overall model fits.

WITHIN-NETWORK CONNECTIVITY

• Estradiol did not predict within-network connectivity.
• Cerebellar DAN (lag 1), VAN (lag 2), and SMN (lag 2) exhibited significant autoregressive effects of network states, with significant model fits for the DAN and VAN.

CONCLUSIONS & FUTURE AIDS

• Serum concentrations of E and P fell within expected ranges and displayed 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 edgewise analyses: Increases in progesterone over time are associated with robust decreases in functional connectivity across the cerebellum.
• Time-synchronous correlational analyses: Increases in estradiol over the cycle are correlated to decreases in functional connectivity across the cerebellum.
• Time-Lagged analyses: Networks exhibit functional stability among metrics of between- and within-network integration.
• Daily hormone levels demonstrate negative associations with cerebellar connectivity, while temporal variability in the cerebellum is attributed more to previous network states rather than estradiol concentrations.