UCSB Academic Senate
Academic Senate Council on Research and Instructional Resources

Application for 2021-22 Faculty Research Grant

APPLICANT INFORMATION

NAME
Emily Jacobs

RANK
Assistant Professor

DEPARTMENT
Psychological and Brain Sciences

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PROJECT INFORMATION

PROJECT TITLE
Applying dense-sampling methods to reveal dynamic endocrine modulation of the nervous system

Amount Requested
$20,000

The Department/Unit that will be receiving/administering the funds:

Financial Coordinator
Kallie Hill

EMAIL ADDRESS
kallie.hill@psych.ucsb.edu

DEPARTMENT

Previous Funding Record for this Project
This is a new project that has not received previous funding support.

Subvention
No.

Past Funding Support from the Academic Senate for Other Projects
I have received funding support from the Senate within the past three fiscal years, and the progress/results and current balance are as described here:

Other Research Support
Start-up Funds: Not answered

I do have other extramural research support.

I have other research support.

Recent Publications
I have recent publications.

Use of Human Subjects
This project involves the use of human subjects, and I understand I must submit an "Application for Approval of Activity Involving the Use of Human Subjects" to the Office of Research prior to starting the project.

Pearl Chase Funds
This proposal is not a request for the Pearl Chase Funds.

Table of Contents

Emily Jacobs, PhD

Applying dense-sampling methods to reveal dynamic endocrine modulation of the nervous system

Sex hormones are powerful neuromodulators of learning and memory, influencing the brain at the level of microscopic intracellular events [1-4] to macroscopic brain organization [5-9]. The major sex steroid hormones, including 17β-estradiol, progesterone, and testosterone, are critical regulators of cell survival and neural plasticity [10]. My laboratory uses brain imaging, endocrine, and computational approaches to understand the extent to which sex hormones influence the structural and functional architecture of the human brain.

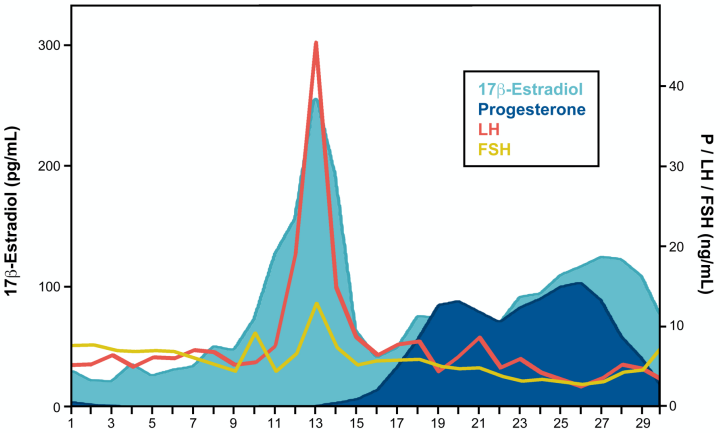


Figure 1. Daily gonadotropin and sex steroid hormone concentrations across a complete menstrual cycle.

Scientists have routinely pushed the bounds of experimental creativity to tease apart the complex nature of brain–hormone interactions. In a new direction for my lab, we address a new set of methodological innovations for probing sex hormone action in the human brain. A central feature of the mammalian endocrine system is that hormone secretion varies over time. For example, during an average human menstrual cycle, spanning 25-32 days, women experience an ~8-fold increase in estradiol and an ~80-fold increase in progesterone (**Fig 1**). Despite this striking change in endocrine status, we lack a complete understanding of how the brain responds to rhythmic changes in hormone production over time. The study of brain–hormone interactions in human neuroscience relies largely on cross-sectional designs that, by nature, cannot capture dynamic changes in hormone production. However, an emerging trend in human neuroimaging is to flip this cross-sectional model by densely sampling individuals over timescales of days, weeks, months, or years to provide greater insight into the *dynamic* properties of the human brain.

To that end, my group recently completed the '**28andMe**' project, in which a female participant underwent brain imaging and venipuncture over 30 consecutive days across a complete menstrual cycle (Study 1), followed by 30 consecutive days on a hormone suppression regimen (Study 2) conducted one year later. The unique strength of these studies derives from their ability to capture, with high spatial and temporal resolution, the brain's response to a central feature of the mammalian endocrine system: hormonal rhythmicity.

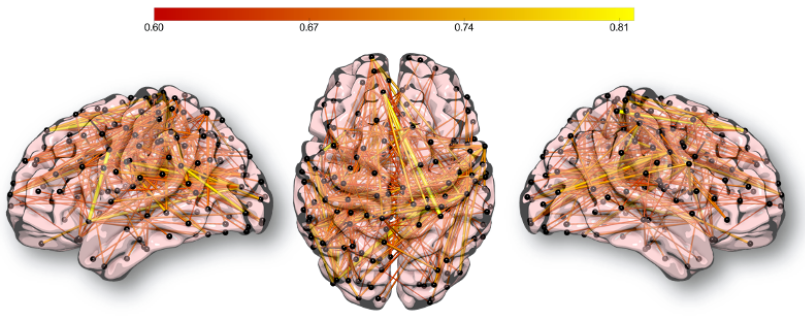
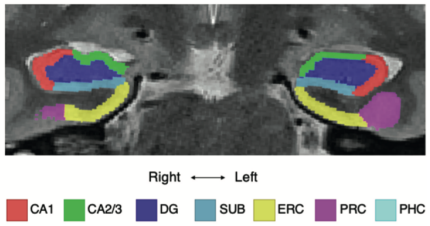


Figure 2. Daily MRI and serological assessments were acquired in a woman across a complete menstrual cycle, allowing us to probe whether day-to-day changes in sex hormones modulate the brain's intrinsic functional network architecture. **Above,** increases in estrogen over time were associated with increased functional connectivity across the whole brain.

Across a series of studies [7, 9, 11-13], we establish the dynamic endocrine modulation of the nervous system. First, we discovered that increases in estrogen are associated with increases in functional connectivity across broad swaths of the cerebral cortex (**Fig 2**). Using time-lagged methods from dynamical systems analysis, we establish estrogen's ability to *drive* widespread patterns of connectivity in the human brain and to enhance the global efficiency of large-scale brain networks.



Next, using high-resolution hippocampal subfield imaging (**left**), we discovered that hormone fluctuations across the cycle and direct pharmacological manipulations alter hippocampal morphology, a brain region densely populated with sex hormone receptors. These results establish sex hormones' ability to dynamically shape brain morphology over rapid time-scales.

This project resulted in a number of publications [7, 9, 11-13] and enhanced our understanding of estrogen and progesterone action in the female brain. *However, we lack critical corresponding data to determine whether sex steroid hormones drive changes in brain structure/function in a densely-sampled male.*

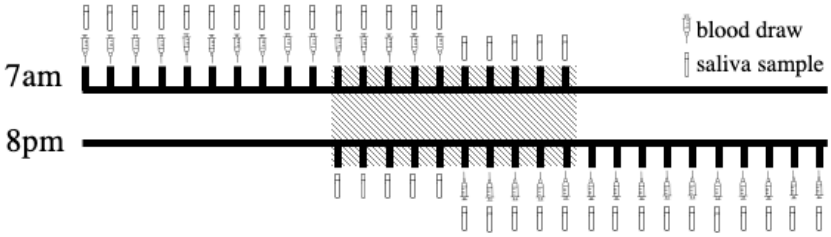


Figure 3. Study timeline for "28andHe". As a sibling study to "28andMe", our new project "28andHe" will densely sample a male participant over 30 days. Daily functional MRI and serological/salivary assessments will be acquired every 12-24 hours for 30 days, with interlocked AM and PM sessions. This will allow us to probe whether diurnal variation in androgens modulate the brain's intrinsic functional network architecture in a male.

In men, sex hormone production follows a daily sinusoidal pattern with a testosterone peak between 6-7am and nadir between 7-8pm. However, no dense-sampling study has captured these diurnal changes to determine testosterone's impact on the brain with high spatiotemporal precision. This is a major oversight that could transform our understanding of testosterone as a rapid neuromodulatory hormone. To that end, this Academic Senate proposal seeks pilot funding to support "**28andHe**", a study that will probe diurnal variation in androgens in a male (**Fig 3**). Funding will support MRI data collection and serological evaluations, acquired every 12-24 hours for 30 consecutive days. This project will address outstanding questions regarding the neuronal impact of day-to-day changes in sex steroid hormones in men, building on the findings that emerged from "28andMe" in a densely-sampled female. A grant from the Academic Senate would provide pilot data and demonstrate feasibility as we look ahead toward securing a federally-funded grant to expand our dense-sampling studies. This initiative is an excellent fit for the National Institute of Mental Health's newly earmarked funding priorities to support dense-sampling MRI, given an increasing recognition that dense-sampling may reveal dynamic properties of the human brain over unprecedented timescales.

References

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10. Galea, L.A.M., Frick, K.M., Hampson, E., Sohrabji, F., Choleris, E., 2017. Why estrogens matter for behavior and brain health. Neuroscience & Biobehavioral Reviews 76, 363–379. https://doi.org/10.1016/j.neubiorev.2016.03.024

11. Mueller J., Pritschet L., Santander T., Taylor C., Grafton S.T. ***Jacobs E.G**., *Carlson J.M. (2021) Dynamic community detection reveals transient reorganization of functional brain network subcommunities across a female menstrual cycle. *(Network Neuroscience) *Co-senior authors*

12. Fitzgerald M., Pritschet L., Santander T., Grafton S.T., **Jacobs E.G**. (2021) Dynamic cerebellar network organization across the human menstrual cycle. *Scientific Reports.*

13. Pritschet L., Taylor C., Santander T., **Jacobs E.G.** (2021) Applying dense-sampling methods to reveal dynamic endocrine modulation of the nervous system. *Current Opinion in Behavioral Science.*

Impact

Scientists have routinely pushed the bounds of experimental creativity to tease apart the complex nature of brain–hormone interactions. Recently, my lab has applied a new set of methodological innovations for probing sex hormone action in the human brain. A central feature of the mammalian endocrine system is that hormone secretion varies over time, and this rhythmicity is essential for sustaining many physiological processes. However, the study of brain–hormone interactions in human neuroscience relies largely on cross-sectional designs that, by nature, cannot capture *dynamic* changes in hormone production. In a series of recent neuroimaging studies, we flipped the cross-sectional model and densely-sampled individuals over timescales of days, weeks, and months to provide greater insight into the dynamic properties of the human brain.

Our '28andMe' project densely sampled a female over a complete menstrual cycle, with MRI and blood draws every 24h for 30 days. The project revealed that endogenous fluctuations in sex hormones shape the structural and functional architecture of the brain over rapid timescales. However, we lack critical corresponding data in a male participant. We seek pilot funds to provide preliminary data and demonstrate feasibility for a study of how diurnal variation in androgens in a male impacts the brain.

In 2020 my lab successfully competed for an R01 from the National Institutes of Health based on work that was first supported by an Academic Senate. Similarly, the proposal described here will provide critical pilot data that will enhance our chances of securing new NIH funding earmarked for dense-sampling MRI studies like the one proposed here.

Principal Investigator: Emily Jacobs
Department: PSYC
Sponsor: Academic Senate Grant
Announcement: 2021

SUPPLIES & OTHER DIRECT COSTS

MRI Scanning	30 hours @ 600/hr	18000.00
Publication Expenses	2,000	2000.00
Phlebotomy/Endocrine Assays	8,000	8000.00

Total 28,000

Budget Justification
The applicant is applying for a 1-year Academic Senate grant. Funding on this project will allow for the collection of preliminary data by supporting MRI expenses and endocrine assays (free and total testosteronne, DHT, SHBG, pituitary gonadotropins)

Personnel:
PI: Emily Jacobs, Ph.D.
Applicant will lead the analysis of the aims outlined in the proposal.

Scanning and endocrine assay expenses will cover data collection for a dense-sampling pilot study, enabling us to provide rigorous preliminary data in support of an NIH R01 targeted for 2022.

Previous Academic Senate Grant Support

I have received previous support from Academic Senate grants, including **"Organizational effects of sex steroid hormones on the maternal brain"** and **"The impact of hormone-based medications on human brain structure and function".** These previous pilot funds were instrumental in securing a large federally funded grant from the National Institutes of Health titled "Impact of gonadal hormone suppression on regional and global brain architecture and cognition" (NIH R01-AG063843).

Some Academic Senate funds from these grants remain and are on track to be expended soon (research efforts for these studies were delayed by COVID-19 related restrictions on human subjects testing but have now resumed). My lab is approved for human subjects testing under the current Stage 4B status.

In addition to extramural grant funding, a number of recent publications were supported by these Academic Senate supported research efforts:

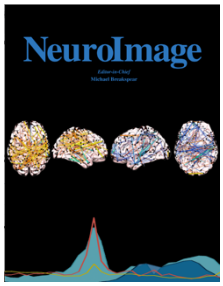
⁺*Trainees*

1. ⁺Pritschet L., ⁺Taylor C., Santander T., **Jacobs E.G.** (2021)Applying dense-sampling methods to reveal dynamic endocrine modulation of the nervous system. *Current Opinions in Behavioral Science.* Special Issue on Deep Imaging, edited by: Caterina Gratton and Rodrigo Braga.

2. ⁺Yu S., Boone A., He C., Davis R., Hegarty M., Chrastil E., **Jacobs E.G.** (In Press) Age related changes in spatial navigation are evident by midlife and differ by sex. *Psychological Science.*

3. ⁺Taylor C., ⁺Pritschet L., & **Jacobs E.G.** (2021) The scientific body of knowledge – whose body does it serve? A spotlight on oral contraceptives and women's health factors in neuroimaging. *Frontiers in Neuroendocrinology (Elsevier Press)* Special Issue "Beyond Sex Differences: A Spotlight on Women's Brain Health"

4. de Lange AG., **Jacobs E.G.**, Galea LAM. (2021) The scientific body of knowledge – whose body does it serve? A spotlight on women's brain health. Editorial in *Frontiers in Neuroendocrinology.* Special Issue "Beyond Sex Differences: A Spotlight on Women's Brain Health"



5. ⁺Pritschet L., Santander T., ⁺Taylor C., Layher E., ⁺Yu S., Miller M.B., Grafton S.T., **Jacobs E.G.** (2020) Functional reorganization of brain networks across the human menstrual cycle. *NeuroImage* 220:117091 ***Cover Image***

6. ⁺Taylor C., ⁺Pritschet L., Olsen R., Layher E., Santander T., Grafton S.T., **Jacobs E.G.** (2020) Progesterone shapes medial temporal lobe volume across the human menstrual cycle. *NeuroImage* 220:117125 ***Featured Review and Editors' Choice*** in *Science*

Translational Medicine. Ref: Stevens J. (2020) Brain structural changes in sync with the cycle 12:553

7. Mueller J., [+]Pritschet L., Santander T., Taylor C., Grafton S.T. ***Jacobs E.G.**, *Carlson J.M. (2021) Dynamic community detection reveals transient reorganization of functional brain network subcommunities across a female menstrual cycle. *(In press – Network Neuroscience) *Co-senior authors*
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8. [+]Fitzgerald M., [+]Pritschet L., Santander T., Grafton S.T., **Jacobs E.G.** (2020) Cerebellar network organization across the human menstrual cycle. *Scientific Reports* 10:20732.

9. Casaletto K, Lindbergh C. et al. (2020) Sexual dimorphism of physical activity on cognitive aging: Role of immune functioning. *Brain, Behavior, and Immunity* 88: 699-710.

10. **Jacobs E.G.** (2020) Why neuroscience needs girls: Gender diversity drives scientific discovery. *Frontiers for Young Minds* 8:37 doi:10.3389/frym.2020.00037

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12. [+]Taylor C., [+]Pritschet L., [+]Yu S., **Jacobs E.G.** (2019) Applying a women's health lens to the study of the aging brain. *Frontiers in Human Neuroscience* doi: 10.3389/fnhum.2019.00224

13. Konishi K, Cherkerzian S, **Jacobs E.G.**, et al. (2019) Impact of adrenal hormones, reproductive aging, and major depression on memory decline in early midlife. *Brain Research* 1721(146303):1-14.

Ongoing Research Support

National Institute of Aging R01-AG063843 *Jacobs and Panizzon (PIs)* *2020-2025*
Impact of gonadal hormone suppression on regional and global brain architecture and cognition
Award: $4,798,062. This research investigates the impact of gonadal hormone suppression on brain structure, function, and cognition in humans undergoing pharmacological treatment for endometriosis.

California Dept. of Public Health 19-10612 *Panizzon (PI) Subaward to Jacobs* 2020
Impact of female reproductive history on Alzheimer's disease risk
Award: $157,365, UCSB subaward: $65,300. This research uses UKBiobank and other population-based datasets to delineate the relationship between early menopause and risk for AD-related brain phenotypes.

UCSB Academic Senate Grant *Jacobs (PI)* *2020*
Organizational effects of sex steroid hormones on the maternal brain
Award: $13,905. This dense-sampling MRI study tracks the neuronal changes that occur across the gestational period before, during, and after pregnancy.

Hellman Family Fellows Fund *Jacobs (PI)* *2019-2020*
Identifying the impact of sex hormone suppression on brain morphology
Award: $40,000. This pilot MRI study investigates the influence of oral hormonal contraceptive use on grey matter volume in young women.

Recent Relevant Publications

[+]*Trainees*

1. [+]Pritschet L., [+]Taylor C., Santander T., **Jacobs E.G.** (2021) Applying dense-sampling methods to reveal dynamic endocrine modulation of the nervous system. *Current Opinions in Behavioral Science.* Special Issue on Deep Imaging, edited by: Caterina Gratton and Rodrigo Braga.

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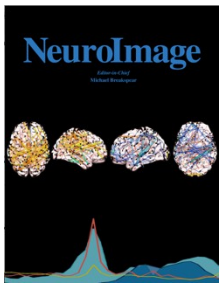

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