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Ovarian Hormones and Their Impacts on Spatial Learning and Navigation

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Psychological and Brain Sciences

by

Alexis Topete

Committee in charge:

Professor Mary Hegarty, Chair

Professor Emily Jacobs

Professor Daniel Montello

Professor Jonathan Schooler

June 2026

The dissertation of Alexis Topete is approved.

Emily Jacobs

Daniel Montello

Jonathan Schooler

Mary Hegarty, Committee Chair

June 2026

Ovarian Hormones and Their Impacts on Spatial Learning and Navigation

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by

Alexis Topete

ACKNOWLEDGMENTS

They say it takes a village to raise a child, and I've come to realize the same goes for raising a PhD student. My village has become vast, now spanning all around the world, and I never realized I could even *know* so many people in my life, let alone have this many backing me these last 6 years. My acknowledgments page could easily be longer than the dissertation itself if I mentioned every single person who has made an impact in my studies, but I have a sincere appreciation for each and every one of them (explicitly mentioned or not).

First, I want to express my sincerest gratitude to my advisor and committee chair, Mary Hegarty. From meeting with me for lunch in 2019 when I was first applying to graduate programs, to printing out all the available resources for student parents at UCSB during interview weekend, to becoming my advocate and mentor these last six years, Mary has been one of the best advisors (if not *the* best) I could have possibly asked for. Aside from caring about research, she has a genuine investment in the wellbeing of her graduate students. I don't know what I would have done without her constant support, encouragement, and patience with me throughout all the many ups and downs in my PhD program. Mary has shown that you really can do it all as a woman in STEM, and I hope to become at least a fraction of the role model to others that Mary has been to me. I also hope to come back for more SCRAMs!

I also want to thank my committee members (Emily Jacobs, Dan Montello, and Jonathan Schooler) for all their insights, feedback, and for directly assisting in securing my post-graduate position. Each person has been on my committee since my qualifying exams almost 4 years ago, and everyone has been integral in my successes as a graduate student. Jonathan has shown me the "big picture" side of research, encouraging me to think outside the box and consider more than just the world of spatial cognition in my research, and backing the ambitious ideas I've had over the course of my studies. Emily has lit my fire for studying women for my dissertation and beyond, and has graciously provided her lab, resources, and support for continuing in the field. Dan has been stellar for grounding me in spatial cognition research, challenging me to consider interdisciplinary perspectives, and overall being a great mentor and resource throughout this PhD.

I can't forget all the people I've encountered in the Spatial Thinking Lab. To all the past and present grad students, Carol He, Chelsie McWhorter, Mitch Munns, and Mable Zhou, you have all had a positive impact on my research and loving the lab I got to work in. I love that I get to say that I've worked on research with all of you, and am excited to continue to collaborate in the future. I also want to extend my appreciation to all the lab managers I've worked with, including Daniel Buonauro, Lane Domke, Dharma Lewis, Isabella Hanken, and Lesli Chaidez, and the many undergraduate research assistants who have been instrumental in getting data collected in the first place – I really couldn't have done it without all of you, and I'll miss you all dearly. I have to give a special shoutout Mable Zhou for filling many roles in my life, including being my first ever undergraduate mentee in 2020, my first Honors student, and finally my colleague when she joined as a graduate student in the lab in 2023.

She's easily surpassed me in excellence, achievement, academic rigor, and all while being quite far from home. I couldn't be prouder, and I can't wait to see her what the future holds.

Despite starting my graduate studies in the middle of the 2020 COVID-19 pandemic, and having the first year and change completely online, I've made so many friends and lasting bonds with the grads in my cohort and throughout the university. An especially big thank you to Anusha Garg, Dylan Benkley, Carly Chak, Hannah Grotzinger, Elle Murata, and Madhuri Kashyap – together we started by suffering through Zoom school while trying to form friendships with each other, to socially-distanced hangouts, to traveling across the world to attend our weddings and celebrate all our life milestones, and finally to graduating (mostly) together. I'm so fortunate to have spent these years with you.

Of course, thank you to the PBS staff that could not have made this degree possible without all of their support and dealing with my constant drop-ins, questions, chats, and anything under the sun. Thank you, Chris McFerron, Katherine Lowe, Joe Jablonski, Shane Zheng, Shannon Rivard, Jenny Gonzalez Hernandez, Laila Elgamiel, and Rosaura Aguirre for all your help throughout the years. I can't imagine a better team for the department.

Thank you to all the other labs and collaborators I've had the pleasure of working with. I want to especially thank Jim Roney for his advice, support, and allowing me to use his lab when I decided I wanted to look at cortisol and ovarian hormone concentrations in my studies. Thank you, Nic Thompson Gonzalez and Amy Boddy, for allowing me to use your wet lab to assay hormones and for being so lovely and generous these past few years. Thank you, Rich Mayer, for giving me critical feedback every quarter on my research and presentations in our weekly shared-lab seminars, and for just being a positive force throughout my time here. Thank you to the collaborators I've had the pleasure of working with outside of UCSB, including John Protzko, Nora Newcombe, Steve Weisberg, Sarah Creem-Regehr, Jeanine Stefanucci, Liz Chrastil, and Hugo Spiers. I've been so fortunate to be a part of a friendly, collaborative area of research.

I want to thank all my family for their love and support as I moved across state lines to pursue my graduate degree. It's been hard to not be within a 30-minute driving distance from everyone, especially with the plethora of life events that have unfolded in these last six years. To my mom Amy, you have been the one rock throughout my life that I could turn to for anything. I could write a book on everything you have done for me, and it still wouldn't cover the love I have for you. From a single, 18-year-old mom to a grandma of six, I'm so fortunate to have been a part of so much of your life and for having you as a mom. To my many siblings, Cody, Morgan, Logan, Zach, and Bella, you've been my best friends and the ones who keep me grounded to family while I've been pursuing my studies. I can't thank you enough for taking the time to FaceTime me and check in, sharing your life events even when I've been bad at reciprocating. It's crazy how much I miss you all, but you still manage to make me feel so loved and so supported through everything. I can't wait to bug you all next time I visit and give all the hugs and cuddles with my nieces and (almost) nephew.

To my grandparents that I was fortunate to move closer to, thank you for your love and support throughout my studies. You have shown a dedicated interest in my studies, asking me the important questions, facilitating thoughtful discussion, and showing unwavering support of all of my endeavors. I have loved getting to spend Easters with you these last few years, and sending you drafts of my papers, knowing that you would actually read through them. You were the family I could turn to and ask advice about graduate school, and kept me rooted in the Topete side by always remembering to send messages for every holiday and birthday. I love you so much, and you have made me so proud to be a Topete. I hope to live up to the name over the course of my life.

I couldn't have gotten through these last few years without my husband, Tikal, and my two girls, Vivian and Lillian. Tikal was the best thing I could have gotten from UCSB, starting as a friend in the cohort to eventually being my life partner and father to Lily. He's demonstrated an immense amount of patience with me as we both went through our graduate studies, from studying for qualifying exams together to getting married and dealing with a pregnancy in our dissertation stages. He is the person who got on a flight at a moment's notice to come be with me when my dad got sick while we were dating, and since then he has been my rock through every funeral, every tear, every issue, and every milestone throughout this PhD. I love you dearly, and I'm so excited to take these next steps with you.

To the girls that make everything worth it, thank you Viv and Lily. Viv has kept me grounded for all of grad school, making sure that I took a break and enjoyed life. From our art projects where we would paint together, to playing games and finding parks and beaches, to helping with math homework and bargaining for the next toy, Viv has kept me in reality and enjoying life. Her curiosity, love, kindness, and patience with me while balancing work and home life has been nothing short of stellar, and she has blossomed into the best big sister that I could ever ask for. Lily, while newer to the scene, has shown me that you don't have to pause on life while furthering your career, and her bubbly personality and overall happy temperament has kept me sane throughout these final stages of the PhD. I can't thank these two enough for letting me be their mom.

To my chosen dad, Shane, I wish you could have been here to finally see me graduate and end my schooling. Losing you halfway through graduate school was the harder than any of the milestones I had to go through to get this PhD, but even though you didn't always verbalize it, you always showed that you were my biggest supporter. From buying a wagon from your rival school (my undergraduate institution) to wheel your grandkids around, to driving across state lines to help me move, to being available at a moment's notice whenever I was down, to the weekly FaceTime because you wanted to see me and Viv, you've been the best father figure I could have ever had. You took me in and called me your own as soon as you joined the family, and I can at least take solace in knowing that I can still bring you with me (if only in a necklace) throughout the next stages of life. I love you, I miss you, and thanks for being the best Pop-Pop to my girls.

VITA OF Alexis Topete

June 2026

EDUCATION

- 2020 – 2026** Ph.D. in the Psychological and Brain Sciences, *University of California – Santa Barbara*
Cognition, Perception, and Cognitive Neuroscience
Thesis title: *Ovarian Hormones and Their Impacts on Spatial Learning and Navigation.*
- 2020 – 2023** M.A. in Psychological and Brain Sciences, *University of California – Santa Barbara*
Thesis title: *How Is It Used? Understanding Navigation System Use and its Relation to Spatial Ability.*
- 2016 – 2019** B.S. in Psychology, *University of Utah*
Thesis title: *GPS Reliance and its Effect on Working Memory and Spatial Ability.*
- 2015 – 2016** General Education, *Snow College*

RESEARCH EXPERIENCE

- 2020 – 2026** Graduate Student Researcher, UC Santa Barbara Spatial Thinking Lab (*PI: Dr. Mary Hegarty*)
- *Research Topics:* Navigation in Virtual Environments, GPS Use and Navigation, Individual Differences in Navigation, Human-Computer Interaction, Women's Health, Navigation and the Menstrual Cycle, Endocrine Aging, Cortisol and Navigation, Mental Rotation, Structural Equation Modeling, Cross-Sectioning, Perspective-Taking, Item Response Theory, Factor Analysis
 - *Funding Sources:* National Institute of Health, National Institute of Aging, Office of Naval Research, Institute for Collaborative Biotechnologies, National Science Foundation, UCSB Academic Senate
- 2018 – 2019** Undergraduate Researcher, University of Utah Spatial Cognition and Navigation (SCAN) Lab (*PIs: Dr. Sarah Creem-Regehr & Dr. Jeanine Stefanucci*)
- 2017** Undergraduate Research Assistant, University of Utah Department of Psychology
- Visual Perception and Spatial Cognition (VPSC) Lab (*PIs: Dr. Sarah Creem-Regehr & Dr. Jeanine Stefanucci*)
 - Relationship Decisions Lab (*Dr. Samantha Joel*)
- 2016** Undergraduate Researcher, Snow College (*PI: Dr. Nick Marsing*)

TEACHING EXPERIENCE

- 2021 – 2026** Teaching Assistant, UC Santa Barbara Psychological & Brain Sciences
- PSY 111: Behavioral Neuroscience (*Spring 2026*)
 - PSY 160SK: An Examination of Key Constructs in the Psychological & Brain Sciences (*Winter 2026*)
 - PSY 106: Intro to Biopsychology (*Spring 2025*)
 - PSY 117L: Lab in Memory & Cognition (*Fall 2021, Spring 2023, Spring 2024, & Fall 2024*)
 - PSY 10B: Statistics in Psychological & Brain Sciences (*Spring 2022 & Winter 2023*)
- 2024** Teaching Associate, UC Santa Barbara Psychological & Brain Sciences
- PSY 108: Cognitive Psychology (*Summer 2024*)
- 2022 – 2023** Lab Course Coordinator, UC Santa Barbara Psychological & Brain Sciences
- PSY 118L: Lab in Attention (*Fall 2022*)
 - PSY 129L: Lab in Perception (*Winter 2023*)
 - PSY 117L: Lab in Memory & Cognition (*Spring 2023*)

PUBLISHED & SUBMITTED MANUSCRIPTS

- Munns, M. E., Nelson, M., He, C., **Topete, A.**, Rashidi, M., Chrastil, E. R., & Hegarty, M. (in revision). *Navigation Ability is Associated with Video Game Experience but not with Other Everyday Spatial Activities*. Manuscript in revision
- Zhou, M., He, C., **Topete, A.**, Munns, M., & Hegarty, M. (2026). Wayfinding strategies in an outdoor environment: Effects of global landmarks, configural knowledge, and spatial anxiety. *Spatial Cognition & Computation*, 1-28. <https://doi.org/10.1080/13875868.2026.2650274>
- Hegarty, M., **Topete, A.**, Zhou, M., Munns, M. E., & Mayer, B. (2026). In J. Plass, R. E. Mayer, & Makransky, G. (Eds.). Learning spatial layouts in virtual reality. *Handbook of Learning in Virtual Reality* (in press). MIT Press.
- Topete, A.**, He, C., & Hegarty, M. (2025). Learning the layout of different environments: Common or dissociated abilities? *Cognitive Research: Principles & Implications*, 10, 6. <https://doi.org/10.1186/s41235-025-00618-5>
- Topete, A.**, He, C., Protzko, J., Schooler, J., & Hegarty, M. (2024). How is GPS used? Understanding navigation system use and its relation to spatial ability. *Cognitive Research: Principles & Implications*, 9, 16. <https://doi.org/10.1186/s41235-024-00545-x>
- Munns, M. E., He, C., **Topete, A.**, & Hegarty, M. (2023). Visualizing cross-sections of 3D objects: Developing efficient measures using item response theory. *Journal of Intelligence*, 11(11), 205. <https://doi.org/10.3390/jintelligence11110205>

MANUSCRIPTS IN PREPARATION

- Topete, A.**, Munns, M. E., Chaidez, L., Newcombe, N. S., Weisberg, S. M., & Hegarty, M. (in prep). *Developing and Validating an Efficient Measure of Navigation Ability*. Manuscript in preparation.
- Topete, A.**, Catena, T., & Hegarty, M. (in prep). *Interface, but not Environment Size, Affects Learning in Virtual Environments*. Manuscript in preparation.
- He, C.,* **Topete, A.***, Protzko, J., Schooler, J., & Hegarty, M. (in prep). *Does GPS Use Impair Navigation Skills? Insights from a Cohort Analysis*. Manuscript in preparation. *Denotes equal authorship.

CONFERENCE PRESENTATIONS AND INVITED TALKS

ORAL PRESENTATIONS AND INVITED TALKS

- Topete, A.** (2026). *Spatial Cognition Guest Lecture*. Invited guest lecturer for a Cognitive Psychology course, Colby College (virtual).
- Topete, A.**, He, C., & Hegarty, M. (2024). *Learning the Layout of Different Environments: Common or Dissociated Abilities?* Symposium talk presented at Spatial Cognition 2024, Dublin, Ireland.
- Munns, M., **Topete, A.**, Weisberg, S., Newcombe, N., & Hegarty, M. (2024). *Measuring Individual Differences in Navigation: Refining the Virtual SILCton Task with Item Response Theory*. Talk presented at Spatial Cognition 2024, Dublin, Ireland.
- Hegarty, M., **Topete, A.**, & He, C. (2023). *Learning the Layout of Different Environments: Common or Dissociated Abilities?* Talk presented at the Psychonomic Society 64th Annual Meeting, San Francisco, CA.
- Topete, A.**, He, C., & Hegarty, M. (2023). *Video Game Experience and its Association to Navigation Performance Across 3 Virtual Environments*. Talk presented at the Symposium for Individual Differences in Cognition 2023, San Francisco, CA.

Topete, A. (2023). *Does Context Matter? Navigation Ability in Different Environment Types*. Talk presented at the UCSB Psychological & Brain Sciences Cognition, Perception, and Cognitive Neuroscience (CPCN) Seminar, Santa Barbara, CA.

Kunz, A. (2022). *How is it Used? Understanding GPS Use and its Relation to Spatial Ability*. Talk presented at the UCSB Psychological & Brain Sciences 2022 Mini-Conference, Santa Barbara, CA.

Kunz, A. (2021). *GPS Usage and Its Effect on Spatial Navigation*. Talk presented at the UCSB Center for Spatial Studies 2021 Spatial Lightning Talks, Santa Barbara, CA.

POSTER PRESENTATIONS

Topete, A., Catena, T., & Hegarty, M. (2026). *Variations in Large- and Small-Scale Spatial Abilities Across the Menstrual Cycle*. Abstract accepted for the 6th Interdisciplinary Navigation Symposium.

Topete, A., Catena, T., & Hegarty, M. (2025). *Comparing Navigation Ability in Desktop and Ambulatory Immersive Virtual Environments*. Psychonomic Society 66th Annual Meeting, Denver, CO.

Topete, A., Munns, M. E., Chaidez, L., Weisberg, S. M., & Hegarty, M. (2025). *Developing and Validating an Efficient Measure of Navigation Ability*. 2025 Symposium for Individual Differences in Cognition, Denver, CO.

Catena, T., **Topete, A., & Roney, J.** (2025). *The Influence of Ambulation on Spatial Exploration and Learning in Immersive Virtual Reality*. 2025 Symposium for Individual Differences in Cognition, Denver, CO.

Topete, A., Catena, T., & Hegarty, M. (2025). *Comparing Navigation in Immersive and Desktop VR Environments*. Cognitive Science Society 2025 Conference, San Francisco, CA.

Topete, A., He, C., & Hegarty, M. (2024). *Navigating in Different Environments: Does Context Matter?* 5th Interdisciplinary Navigation Symposium, Merano, Italy.

Hegarty, M., **Topete, A., & Munns, M.** (2023). *Comprehensive Spatial Testing for Selection and Training*. Office of Naval Research Fall 2023 Technical Review for Decision Making and Expertise Development, Quantico, VA.

Zhou, M., He, C., **Kunz, A., Munns, M., & Hegarty, M.** (2023). *Outdoor Navigation: Learning, Strategies, and Influence of Distal Landmarks*. 2023 International Conference on Learning and Memory, Huntington Beach, CA.

Munns, M., **Kunz, A., He, C., & Hegarty, M.** (2022). *Measures of Visualizing Cross Sections of 3D Objects: An Assessment Using Item Response Theory*. Psychonomic Society 63rd Annual Meeting, Boston, MA.

Kunz, A., He, C., Protzko, J., Schooler, J., & Hegarty, M. (2022). *Relations Between Spatial Ability and Uses of GPS*. Psychonomic Society 63rd Annual Meeting, Boston, MA.

Kunz, A., He, C., Protzko, J., Schooler, J., & Hegarty, M. (2022). *GPS Usages and Their Relations to Spatial Ability and Scenario Familiarity*. 4th Interdisciplinary Navigation Symposium (virtual).

He, C., Protzko, J., **Kunz, A., Schooler, J., & Hegarty, M.** (2021). *Does GPS Use Impair Navigation Skills? Insights from a Cohort Analysis*. 8th International Conference on Spatial Cognition (virtual).

Kunz, A., He, C., Protzko, J., Schooler, J., & Hegarty, M. (2021). *Different Perspectives: How Spatial Dispositions and Navigation Scenarios Affect Use of GPS Functionalities*. Psychonomic Society 62nd Annual Meeting (virtual).

He, C., Protzko, J., **Kunz, A., Schooler, J., & Hegarty, M.** (2021). *Does GPS Use Impair Navigation Skills? Insights from a Cohort Analysis*. Psychonomic Society 62nd Annual Meeting (virtual).

He, C., Protzko, J., **Kunz, A., Schooler, J., & Hegarty, M.** (2021). *Does GPS Use Impair Navigation Skills? Insights from a Cohort Analysis*. [Spatial@UCSB.Global2021](#): Spatial Data Science for a Sustainable Future (virtual).

- He, C., Protzko, J., **Kunz, A.**, Schooler, J., & Hegarty, M. (2021). *Does GPS Use Impair Navigation Skills? Insights from a Cohort Analysis*. 2021 Association for Psychological Science Virtual Convention.
- Kunz, A.T.**, Ruginski, I.T., & Rand, K. (2019). *GPS Reliance and Its Effect on Working Memory and Spatial Ability*. University of Utah's 2019 Summer Symposium, Salt Lake City, UT.
- Kunz, A.T.**, Ruginski, I.T., & Rand, K. (2019). *GPS Reliance and Its Effect on Working Memory and Spatial Ability*. University of Utah 2019 CSBS Student Research Day, Salt Lake City, UT.
- Marsing, N., Bradley, S. Slaughter, K., Nixon, B., Luck, S., **Topete, A.**, & Unsworth, A. (2016). *When Does Mutual Gaze Become Uncomfortable?* 2016 Rocky Mountain Psychological Association Conference, Denver, CO.

GRANTS

*Direct costs, †Total costs.

CURRENT

2025 – 2026 *Elucidating the Influence of Ovarian Aging and Endocrine Shifts on Spatial Navigation, as an Early Diagnostic Target for Alzheimer's Disease*. (NIH 1F99AG095134-01). **Principal Investigator** with Sponsor Hegarty.

LEADERSHIP EXPERIENCE

- 2022 – 2025** President, UC Santa Barbara ACCESS GRADS Program
- Worked alongside UCSB's Promise Scholars Program to reach high-risk underrepresented students and provide access to dedicated mentorship
 - Assisted with the expansion of the program to other universities (UC Davis)
 - Co-developed the program's first standardized Statement of Purpose, recruitment templates, and forms for assessing program success
 - Co-wrote and obtained grants to obtain funding for the program and encourage greater recruitment efforts
- 2021 – 2022** Event Coordinator, UC Santa Barbara ACCESS GRADS Program
- Developed, created, and presented the program's first iteration of a 3-part "Applying to Graduate School" series
 - Graduate Application Materials in Psychology (*Winter 2022*)
 - Graduate Interviews and Decisions (*Winter 2022*)
 - Faculty Q&A on Applying to Graduate School (*Spring 2022*)

MENTORSHIP EXPERIENCE

- 2021 – 2026** Graduate Supervisor/Mentor, UC Santa Barbara Undergraduate Honors Thesis & Undergraduate Research & Creative Activities (URCA) Project
- Amelia Chen (URCA Project): *Cortisol & Spatial Navigation in Immersive and Desktop VR*. Finalist in the URCA Slam contest (2026)
 - Eva Madell (Honors Project): *Executive Control of Bilingual Individuals*; recipient of the UCSB URCA Grant (\$720)
 - Tvisha Patel (Honors Project): *The Effect of Button Design on Website Navigation Efficiency*; recipient of the UCSB URCA Grant (\$720)
 - William Zhang (Honors Project): *The Effect of Video Game Experience on Large-Scale Spatial Abilities*.
 - Aneri Bhatt (Honors Project): *The Impact of Progesterone Use on Spatial Navigation Strategy and Hippocampal Structure*; recipient of the UCSB URCA Activities Grant (\$750)

- Mable Zhou (Honors Project): *Influence of Distal Cues on Spatial Knowledge Acquisition in an Outdoor Environment*; recipient of the UCSB URCA Grant (\$750); awarded the Morgan Award for Research Promise
- 2020 – 2026** Graduate Mentor, UC Santa Barbara ACCESS GRADS Program
- 2025 – 2026** Mentor, UC Santa Barbara's Art and Reproductive Biology Course
- 2023 – 2026** Graduate Mentor, UC Santa Barbara's Teaching Assistant Advisory Program
- 2023 – 2025** Advanced Graduate Mentor, UC Santa Barbara's Psychological & Brain Sciences
- 2023 – 2024** Advanced Graduate Mentor, UC Santa Barbara's Graduate Scholars Program
- 2021** Graduate Mentor, UC Santa Barbara EUREKA! Program

CERTIFICATIONS

2025	Bloodborne Pathogens Certification, UC Santa Barbara (<i>Expires December 2026</i>)
2024	Responsible Conduct of Research – Social and Behavioral Certification, CITI (<i>Expires September 2029</i>)
2024	Summer Teaching Institute for Associates (STIA) Certification, UC Santa Barbara
2023	Social and Behavioral Research – Refresher, CITI (<i>Expires September 2026</i>)
2020	Research Core (CoreXM) Expert Certification, Qualtrics
2020	Employee Experience Expert Certification, Qualtrics
2020	Customer Experience Expert Certification, Qualtrics
2020	Research Core (CoreXM) Certification, Qualtrics
2019	Human Factors Certification, University of Utah

HONORS AND AWARDS

2026	Training and Community Outreach (TACO) Grad & Post-Doc STEM Grants, UCSB Center for Science & Engineering Partnerships (CSEP): \$500 awarded to host a Reproductive Biology & Art Showcase
2025	Doctoral Student Travel Grant, UCSB Academic Senate: \$900 awarded to present at the Psychonomic Society 66 th Annual Meeting in Denver, Colorado.
2025	Graduate Division Dissertation Fellowship: \$10,834 stipend awarded for the Fall 2025 academic quarter including tuition and health insurance, UC Santa Barbara
2025	Graduate Division Decolvenaere Research Accelerator Award: \$8,000 stipend awarded in Summer 2025 to provide funding for dissertation research supplies, UC Santa Barbara
2024 – 2025	TACO Grad & Post-Doc STEM Grants, UCSB CSEP: \$1,150 awarded to host Access Grads' Applying to Graduate School 3-Part Series over 2 years
2024	APA Commission on Ethnic Minority Recruitment, Retention, and Training in Psychology II (CEMRRAT) Task Force Implementation Grant: \$5,475 awarded to Access Grads under the Undergraduate/Graduate Innovation area.
2024	Summer Travel Grant, UCSB Graduate Student Association: \$500 awarded for presenting research at the 5 th Interdisciplinary Navigation Symposium in Merano, Italy
2024	Student Travel Grant, UCSB Psychological & Brain Sciences: \$500 awarded to present research at the 5 th Interdisciplinary Navigation Symposium in Merano, Italy
2024	Doctoral Student Travel Grant, UCSB Academic Senate: \$1,500 awarded to present at the 5 th Interdisciplinary Navigation Symposium in Merano, Italy
2021	Family Care Grant, Psychonomic Society
2020 – 2021	Regent's Fellowship: \$29,000 stipend awarded for the 2020-2021 academic year including tuition and health insurance, UC Santa Barbara
2019	Undergraduate Research Scholar Designation, University of Utah
2017 – 2019	Dean's List, University of Utah (<i>Fall 2017 – Spring 2019</i>)
2015 – 2016	Academic Elite Scholarship, Snow College

2015 Dean's List, Snow College (*Fall 2015*)

PRESS COVERAGE

August 2024 Estos son los efectos nocivos que causa el GPS al cerebro, según múltiples estudios.
La Nación.

PROFESSIONAL AND COMMITTEE EXPERIENCE

2025 – Present Advisory Board Member, KNOWN menstrual cycle tracking application
2022 – 2026 Undergraduate Curriculum Committee Graduate Student Representative, UC Santa Barbara Psychological & Brain Sciences
2019 – 2020 Qualtrics Research Services Opportunity Fulfillment Representative, Level 2
▪ *Councils:* Service Delivery Council member

COMMUNITY SERVICE EXPERIENCE

2026 Facilitator, UCSB Undergraduate Research & Creative Activities (URCA) Conference
2025 – 2026 Reviewer, *Journal of Environmental Psychology*
2025 Reviewer, *IEEE VR 2026*
Winter 2023 Graduate Student Organizer for UCSB Psychological & Brain Sciences' Cognition, Perception, and Cognitive Neuroscience Graduate Interview Weekend
2018 – 2021 Elected State Delegate for a three-year term representing Herriman, Utah

PROFESSIONAL MEMBERSHIPS

2022 – Present Student Member, Royal Institute of Navigation
2022 – Present Member, Womxn in Science & Engineering
2020 – Present Member, Psychonomic Society
2020 – Present Member, Cognitive Science Society (*2020-2021, 2025-Present*)
2023 – 2024 Graduate Student Member, American Psychological Association
2021 – 2023 Graduate Student Affiliate, Association for Psychological Science

ABSTRACT

Ovarian Hormones and Their Impacts on Spatial Learning and Navigation

by

Alexis Topete

Although women account for over half of the world's population, there has been little work devoted to studying women's health and cognition, especially from an endocrine perspective. This is particularly striking when changes in ovarian hormones (such as during menopause) are assumed to play a role in the risk of developing severe cognitive impairments, such as Alzheimer's Disease. Navigation ability is one of the first cognitive abilities to deteriorate in early Alzheimer's, women account for 2/3rds of all late-onset cases, and the risk for developing Alzheimer's significantly increases after menopause. As such, it is important to understand how ovarian hormones are associated with the ability to navigate, as this can be a crucial marker for detecting early, more preventable stages of Alzheimer's.

Animal research has previously demonstrated positive effects of estradiol on navigation, especially on the ability to take novel, more efficient shortcuts (i.e., a *place-based* strategy) compared to previously learned, less efficient routes when wayfinding (i.e., a *response-based* strategy). However, little work has examined these effects in humans, and the work that has been conducted on ovarian hormones and spatial abilities has been primarily dedicated to small-scale spatial abilities, such as the ability to mentally rotate objects, rather than large-scale navigation ability. This dissertation investigates how hormones are associated with navigation ability and strategy in young adult women after learning the layout of a novel environment.

Chapter I serves as an introduction to the dissertation, reviewing the literature on the history of spatial cognition research, sex differences in navigation, the brain and navigation, and what we know about ovarian hormones and navigation ability (from human and rodent studies). Chapter II develops the navigation task used in this research, which involves learning the layout of a novel environment and first examines the way in which we measure spatial learning in immersive and desktop virtual reality (VR) environments. In this chapter, Study 1 takes a within-subjects approach to examine if spatial learning is similar in desktop and immersive maze environments that are identical in relative structure and learning experience. Study 2, conducted between-subjects, examines spatial knowledge acquisition in identical maze environments that vary by interface (immersive ambulatory or desktop VR) and/or scale (10 x 10m or 55 x 55m).

Across these studies, we found that while performance (via pointing and wayfinding efficiency) was significantly correlated across immersive and desktop interfaces, pointing performance (a measure of survey knowledge) was better in immersive VR than desktop possibly due to the inclusion of body-based cues from locomotion. However, wayfinding efficiency did not significantly differ between interfaces. We also found that the environment size did not impact spatial learning. These results collectively provide a bridge between Chapters III and IV, as these differed in the interface used to administer the tasks (immersive in Chapter III, desktop in Chapter IV).

Chapter III examines effects of estradiol on navigation across the menstrual cycle, assessing navigation ability and strategy in young, naturally-cycling women in high estradiol (ovulatory window) and low estradiol (early follicular/menses) phases. This study takes a within-subjects approach, using immersive virtual reality environments to measure

wayfinding efficiency, navigation strategy and onsite pointing ability, as well as a small-scale mental rotation task and general cognitive ability. Results indicate that women in the ovulatory window (when estradiol is high) had better pointing ability than when they were in the early follicular/menses phase (when estradiol is low), but contrary to previous hypotheses, there were no significant differences between cycle phase in wayfinding efficiency or navigation strategy. We additionally did not find any differences in mental rotation or general cognitive ability (e.g., processing speed, executive function, working memory, episodic memory, inhibition) across cycle phases.

Chapter IV investigates chemically-induced ovarian hormone suppression on navigation ability in young adult women. A cohort of young, premenopausal women had ovarian hormones chemically suppressed for at least 3 months as a treatment for endometriosis (Cases). Age-matched young women, who did not undergo ovarian hormone suppression, were included to serve as a control group. Women were tested on navigation ability and strategy use in a desktop maze both before treatment (BL), and 3 months following onset of treatment (T3). We also measured a face-name associative memory task, as an additional measure of hippocampal function. In contrast to hypotheses, both groups significantly improved in performance over time in both wayfinding efficiency and place-based strategy use, and in the case of efficiency, Cases had relatively greater improvement over time (possibly due to minimized chronic pain or greater room for improvement). However, poorer pre-test (BL) performance for women with endometriosis (relative to their control counterparts) may be in part explained by impacts of chronic pain prior to treatment.

Finally, Chapter V addresses the contribution of the studies in this dissertation, including the distinction between graph and survey knowledge acquisition in different

interfaces and how spatial learning and navigation are influenced by changes in ovarian hormones, both at shorter- and longer-term timescales.

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I. GENERAL INTRODUCTION

Navigating from one place to another is an unavoidable component of life, and being able to successfully travel from one place to another — such as walking throughout your neighborhood or determining a shortcut on the way home to avoid rush hour — is an ability that is not only crucial for day-to-day functioning, but is also often overlooked in cognitive science research.

This dissertation examines the role of ovarian hormones in navigation performance and strategy use. To introduce the studies, I first review the early history of research on human navigation, and how sex differences in navigation have been traditionally measured. I then briefly discuss the brain as it relates to navigation, ovarian hormones and endocrine aging in regards to spatial cognition and navigation ability, methodological considerations for studying navigation ability and strategy, and identify current gaps in the literature. These topics collectively frame Chapter I as an introduction to my experimental studies.

History of Spatial Cognition and Early Studies on Individual Differences in Spatial Cognition

The field of spatial cognition is still relatively new, with the earliest formalized research dating to the early to mid-20th century. Early work noted descriptions of disorientation, or “illusions of orientation” as an area deserving devoted study (Binet, 1894), and highlighted the importance of considering the orientation and construction of physical maps as a tool for better aiding navigation, especially when teaching children (Gulliver, 1908; Ridgley, 1922). Aside from physical map education, Trowbridge (1913) coined the term “imaginary map” as the mental representations one creates, distinguished by either egocentric (relative to cardinal directions) or domicentric maps (relative to a fixed reference

point, usually the home). While earlier work dedicated to studying orientation was conducted by geographers (e.g., Howe, 1931; Howe, 1932; Lord, 1941), psychologists began to focus on orientation and navigation more formally in the late 1930s to early 1940s (e.g., Ryan & Ryan, 1940; Yoshioka, 1942; Piaget & Inhelder, 1948/1967).

The ability to form an accurate internal representation of a spatial layout was further defined by Edward Tolman via a series of rodent (rat) studies, referring to this as someone's ability to construct a *cognitive map* (1948). Accurate construction of a cognitive map has been primarily assumed to be synonymous with acquiring *survey knowledge* of an environment, which contains relatively accurate metric information about the spatial layout of an environment, and is defined as configurations of some combination of points (places and locations), lines (e.g., routes, paths), areas (regions and districts), and surfaces (Golledge, 1999). It is to be noted, however, that the term "cognitive map" is simply that – just a term. Other works consider it more as symbolic and more generalizable, and allow cognitive maps to be route-like, schematic, and non-metric in nature (e.g., Kitchin, 2001; Gallistel, 2008). For simplicity's sake the term cognitive map will be used as an analogue to survey knowledge throughout this dissertation, but is worth making the brief distinction.

One of the first theoretical frameworks of environmental spatial development, or microgenesis (Siegel & White, 1975), assumed that acquisition of survey knowledge is a sequential process – first beginning with *landmark knowledge*, or the knowledge of landmarks in a given environment, followed by *route knowledge*, usually assumed to be a more procedural ability to navigate to landmarks using routes that have been previously traversed, and finally *survey knowledge*, where metric information is obtained about an environment and between various landmarks, allowing one to successfully travel from one

place to another without the reliance of traveling a given route before. It is to be noted that in more recent research, another type of spatial knowledge, *graph knowledge*, has been proposed as an intermediary between route and survey knowledge, consisting of topological path relations between locations and landmarks in an environment beyond the originally experienced paths (like survey knowledge), but, unlike survey knowledge, does not contain explicit metric information about distances or directions (Kuipers, 2000; Chrastil & Warren, 2015).

In earlier research, Siegel and White's (1975) framework was generally supported. For example, Thorndyke and Hayes-Roth found that, when there is little to moderate exposure to an environment, learning via a map is better for tasks that require survey knowledge, compared to direct experience (i.e., actual navigation in an environment) which is better for tasks that require route knowledge. However, once extensive exposure has been achieved, the advantage of the map vanishes, showing that direct experience when learning an environment likely follows the same, sequential process (1982). The acquisition of survey knowledge has additionally been tested via *route-integration paradigms*, where participants first navigate through two routes that are separate from each other, and then exposed to a third, connecting route that allows the participant to integrate the first two routes together. Early work has found that, while the connecting route allows people to establish survey knowledge to be able to point to landmarks that were not within the original routes (i.e., were between-route landmark trials), pointing ability is both slower and less accurate than within-route landmark trials (Montello & Pick, 1993).

Despite the useful approach of Siegel & White's initial framework for designing studies to test spatial knowledge acquisition, navigation ability turned out to be far more

complex. A new framework challenging the previous dominant framework was proposed by Montello (1998) – rather than types spatial knowledge being derived in a sequential manner, as previously assumed, it was argued that *all* types of spatial knowledge begin developing as early as the first exposure to an environment, continuously progress in completeness with additional exposure, and individuals will differ in the extent to which they gain knowledge with exposure.

The first empirical test between the dominant (Siegel & White, 1972) and new framework (Montello, 1998) was conducted by Ishikawa & Montello (2006), where participants learned an environment via a route-integration paradigm. In this study, participants were first directed through two separate routes in a neighborhood with a complex layout for 4 weeks, and then exposed to a connecting route for weeks 5-10. The idea of the study was that, over the course of 10 weeks, participants should demonstrate a transition from landmark knowledge, to route knowledge, and finally survey knowledge.

However, the researchers found that while some participants acquired knowledge sequentially, there were also many participants that did not fall within Siegel & White's framework expectations (1975). Other groups of navigators did not sequentially gain different types of spatial knowledge – one group was able to construct an accurate cognitive map of the environment after only one exposure to the connecting route, and another group was only able to attain route knowledge, no matter how many times they were exposed to the connecting route. This was one of the first studies assessing individual differences in navigation ability from a longitudinal perspective, showing that acquisition of survey knowledge is not guaranteed in all individuals, and there are varying rates in which it can be acquired. This partially supported the framework established by Montello (1998), in which

individuals can develop survey knowledge very quickly rather than via a series of sequential steps in knowledge acquisition. The methodologies for this route-integration paradigm were adopted when establishing a more recent, widely-available desktop environment and tasks (e.g., Schinazi et al., 2013; Weisberg et al., 2014), where participants first learn two initial routes, and then are introduced to a connecting route (in this case, two connecting routes) to measure acquisition of route and survey knowledge information.

Aside from finding that individual differences exist in general navigation for types of acquired knowledge, work in the early 2000s additionally established important findings for measuring spatial ability, both between small and large-scale abilities, and the mode in which tasks are administered. In a large study conducted by Hegarty and colleagues (2006), participants were tasked with learning the layout of three different environments (one by direct experience, one by desktop navigation, and one by watching a video recording of the environment), as well as various measures of small-scale spatial ability (e.g., perspective taking, mental rotation, embedded figures, and an arrow span task), self-reported sense of direction, and general verbal abilities. Their findings were that the mode in which the environment was learned in matters—navigation ability after learning an environment via visual learning (i.e., either via desktop or watching a video) had a greater association with small-scale spatial abilities than learning an environment via direct experience, and was less correlated with self-reported sense of direction. This partial dissociation between methods of learning shed some early light into the considerations of measuring navigation ability, and potential implications in individual differences research.

Other research conducted on individual differences was dedicated to other aspects of spatial cognition, such as self-reported sense of direction (Kozlowski & Bryant, 1977;

Hegarty et al., 2002) and spatial anxiety (Lawton, 1994), perspective taking compared to spatial visualization (Kozhenikov & Hegarty, 2001) and mental rotation ability (Hegarty & Waller, 2004), as well as other aspects of small-scale spatial cognition (see Hegarty & Waller, 2005 for a review). Prior to Ishikawa & Montello's study (2006), a fair amount of research examining navigation ability examined how individual differences in small-scale spatial abilities (Hegarty & Waller, 2005; Fields & Shelton, 2006; Pazzaglia & De Beni, 2001; Lorenz & Neisser, 1986; Allen et al., 1996) and sex differences (Montello et al., 1999; Sandstrom, Kaufman, & Huettel, 1998) were related to acquisition of spatial knowledge. This body of research showed a few key findings for individual differences in navigation. First, when it comes to small-scale spatial cognition, the ability to take on different perspectives is generally more positively associated with navigation ability than a measure of object-based performance, such as mental rotation ability. Second, there are prominent sex differences in navigation ability, where men generally tend to outperform women in tasks that require a better cognitive map, or acquired survey knowledge, whereas women perform better in static object-based spatial memory and route knowledge tasks.

Sex Differences in Navigation Ability

Sex differences are an important component of individual differences in navigation ability. There has been a vast body of work showing that, while sex differences do not seem to be very prominent before the age of 13, by puberty through adulthood men tend to outperform women in navigation tasks that are dependent on acquired survey knowledge with small to medium effect sizes (see Nazareth et al., 2019 for a review). More specifically, men tend to outperform women in wayfinding efficiency (Boone, Gong, & Hegarty., 2018; Montello et al., 1999; Boone, Maghen, & Hegarty, 2019) and the ability to identify and point

to the locations of various landmarks within the environment after learning routes through the environment (Hegarty et al., 2006), take more shortcuts over learned, less efficient routes (Boone et al., 2018, Boone et al., 2019), use distal cues more frequently when traversing through environments (Padilla et al., 2017; Sandstrom, Kaufman, & Huettel, 1998), and cover more distance when exploring new environments (Gagnon et al., 2018). However, it is noted that when measuring navigation strategy, while still significant, sex differences are less pronounced when the instructions are to take the shortest path compared to instructions that do not specify how to navigate (Boone et al., 2019). More specifically, men tend to prefer using *place-based strategies* (taking novel, more efficient shortcuts, indicative of acquired survey knowledge) whereas women tend to prefer using *route/response-based strategies* (taking exact routes that have been previously learned before, indicative of acquired route knowledge) in navigation, but women will increase use of place-based strategies when explicitly tasked with taking the shortest path. This suggests that women do acquire survey knowledge to a greater extent than has been previously measured, but choose not to take the shortest path and instead *prefer* to utilize route knowledge (indicating that strategy selection may be a prominent driver of sex differences in navigation). These differences in navigation strategy could possibly be due to women having higher self-reported spatial anxiety than men (Lawton, 1994), but the work conducted in this specific domain is limited (e.g., Varshney, Munns, et al., 2024; Zhou et al., 2026).

While men tend to outperform women in most tasks that require survey knowledge or the construction of a cognitive map, women show an advantage in spatial memory tasks that involve remembering the locations of objects in an array, and this advantage begins around puberty (Silverman & Eals, 1992). More specifically, women generally outperform men in

object identity and object location memory after roughly the age of 13, and effect sizes stay relatively stable (see Voyer et al., 2007 for a meta-analysis). In another study conducted by New and colleagues (2007), a situation was demonstrated in which women were shown to have the advantage in an object-location memory task. Referred to as the “Farmer’s Market” study, men and women at a farmer’s market in Santa Barbara were tested on their ability to memorize the location of various foods in the market’s array of booths. The authors’ hypothesis was that, in ancestral environments, women were more typically involved in gathering compared to men, who instead were more likely to provision through hunting. Following from this, the researchers hypothesized that women have evolved specific adaptations for acquiring spatial knowledge of static food sources. In such a case, their performance in remembering the location of calorically valuable foods was hypothesized to be better than men’s.

This prediction was confirmed – women had higher pointing accuracy for food items’ locations than men. Additionally, it was found that pointing ability was preferentially attuned to foods with higher caloric density (e.g., the pointing error of olive oil, which has higher caloric density, was significantly lower than pointing error for cucumbers, which has lower caloric density). Evolutionary psychologists have claimed this ability to be reflective of “Gathering Navigation Theory,” where women’s spatial memory is adapted to gathering-type behaviors for static food sources, and this is a chronically active mechanism (Silverman & Eals, 1992; New et al., 2007; Krasnow et al., 2011). It is to be noted, however, that this finding could also be in part influenced by higher caloric density foods being more salient and sparser in farmers markets (i.e., there are likely to be relatively numerous stands that include tomatoes and cucumbers, but few that include honey or olive oil).

In sum, a male advantage is typically observed in navigation tasks that require survey knowledge acquisition. However, this apparent advantage becomes less prominent when participants are explicitly tasked with taking the most efficient path in a wayfinding task, and this may be due to sex differences in preferred navigational strategy—in other words, the strategy of choice may be at least partially attributed to spatial anxiety. Finally, there is likely a female advantage in navigation when the task is based on the static object-location memory, potentially reflecting an evolved cognitive mechanism that is preferentially expressed in women. However, it is noted that when a recent meta-analysis was conducted on spatial navigation abilities, researchers found that there was either a consistent male advantage, or no difference between sexes in various navigation outcome measures, and only ranged in small to medium effect sizes (see Nazareth et al., 2019).

The Brain and Navigation (Brief)

The ability to navigate is relatively complex, relying on various brain structures such as the hippocampus (O'Keefe & Nadel, 1978; Maguire et al., 2006; Byrne et al., 2007; Spiers & Maguire, 2007; Moser et al., 2008; Jacobs et al., 2010; Howard et al., 2014; Lisman et al., 2017; Wagner et al., 2023; Ekstrom & Hill, 2023), retrosplenial cortex (Byrne et al., 2007; Jacobs et al., 2010; Ekstrom et al., 2017; Do et al., 2021; Wagner et al., 2023), entorhinal cortex (Hafting et al., 2005; Moser et al., 2008; Howard et al., 2014; Wagner et al., 2023), and the posterior parietal cortex (Byrne et al., 2007; Spiers & Maguire, 2007; Ekstrom et al., 2017; Rolls, 2023; Wagner et al., 2023). Larger posterior (relative to anterior) hippocampi have been found in those with exceptional navigation abilities, such as London taxi drivers (Maguire et al., 2006), and hippocampus atrophy over time has been associated with episodic memory decline in older age (Gorbach et al., 2017).

The hippocampus is also a region with many estrogen receptors, and loss of the expression of estrogen receptors over time (e.g., with aging) is also marked by cognitive decline in hippocampal function (Bean et al., 2014). Additionally, sex differences exist in hippocampal plasticity and conditions that directly target hippocampal integrity, in that women have more estrogen receptors in the hippocampus relative to men, and are more impacted by tau accumulation in the hippocampus and experience more pronounced effects of cognitive decline (see Yagi & Galea, 2019 for a more extensive review). In summary, neural structures that are implicated in spatial navigation (particularly, the hippocampus) are also structures that vary in function and integrity with sex steroid hormones, particularly estrogen.

Ovarian Hormones and Endocrine Aging in Spatial Cognition and Navigation Ability

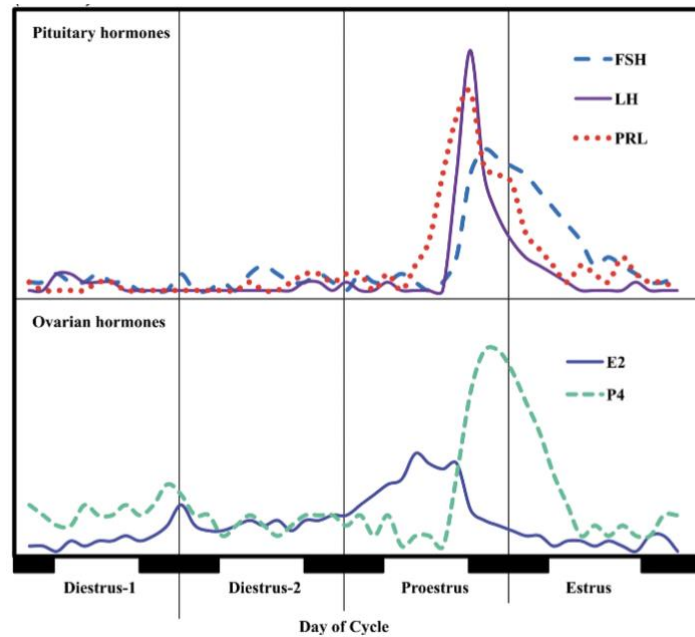
This dissertation examines how ovarian hormone concentrations, and primarily estradiol/estrogen, can account for some of the sex differences found in navigation abilities. First, I will examine what we have learned about ovarian hormones and spatial navigation abilities from animal studies (primarily rats). Then, I will examine what we know to date from human studies, endocrine aging and navigation, and identify gaps in knowledge that form the basis of this dissertation.

Animal Studies. Sex steroids play an interesting role in spatial cognition, and research conducted on female rats has revealed a dynamic interaction between ovarian hormones on navigation behavior. The reproductive cycle in female rats (i.e., the estrous cycle) has four phases over the course of approximately 4-5 days: proestrus, estrus, metestrus/diestrus-1, and diestrus/diestrus-2 (Westwood, 2008). The estrous cycle follows this pattern: there is an increase of 17β -estradiol benzoate (E2) on day 2 of diestrus, with E2 peaking in the middle

of the day of proestrus. Later that same day, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin (PRL) significantly increase, allowing for the quick production and spike in progesterone (P4). Pituitary and ovarian hormones begin to decrease around the late proestrus to mid-estrus stage, leveling out by the end of estrus and into the metestrus phase (see Figure 1, diagrammed by Andersson et al., 2013).

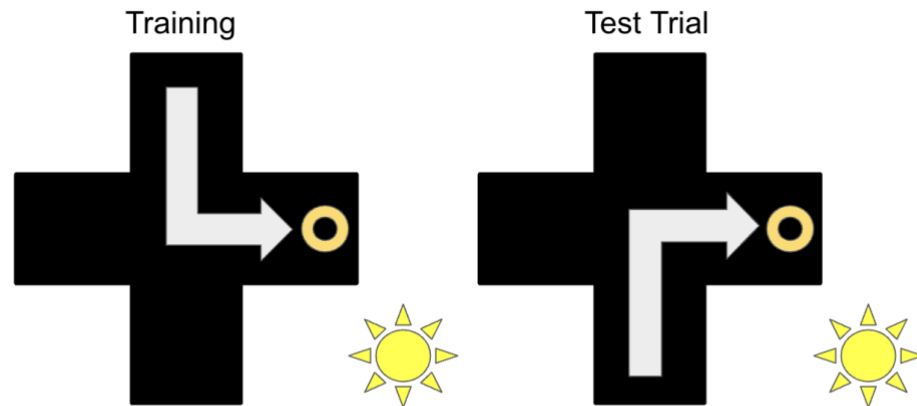
In rodents, the estrous cycle is associated with changes in neural structures implicated in navigation, as well as behavioral strategy shifts in navigation. For example, dendritic spine density in CA1 hippocampal pyramidal cells fluctuate with the estrous cycle in female rats – when E2 is high, spine density increases. However, when E2 is low or P4 is high for a certain length of time, dendritic spine density decreases (Woolley & McEwen, 1993). Since the hippocampus is considered a key brain region for spatial navigation (O'Keefe & Nadel, 1978) and developing cognitive maps (Epstein et al., 2017), it suggests that estradiol may play an important role for navigation ability in women.

Figure 1. Graphical Representation of Hormonal Fluctuations Across the Rat Estrous Cycle (Andersson et al., 2013).



Navigation strategy use in rats is typically measured via a dual solution plus- or T-maze environment, in which rats are first placed in one arm of the maze, and trained to find the location of a goal arm to a food reward from that starting position. After the training period, strategy use is measured by either turning the maze 180 degrees (for a T-maze) or by placing the rat in the arm directly opposite to the arm they were originally trained in (for a plus maze), and measuring if the rat uses a response-based strategy (i.e., using egocentric cues and turning based on where the reward was relative to their body position, such as left or right), or a place-based strategy (i.e., relying on allocentric, extramaze cues to infer the direction to a food reward), see Figure 2 for a graphical interpretation of the plus maze.

Figure 2. Graphical Representation of a Standard Plus Maze Environment Training and Testing Trial.



In rat studies directly involving navigation, one study found that administering E2 to ovariectomized female rats 24 hours before learning a task improved their performance (compared to ovariectomized controls) in a plus-maze task requiring place-based strategies, but hindered performance when the task required using response-based strategies (Korol & Kolo, 2002). Additionally, when assessing dosage of E2 administered, it was found that giving ovariectomized female rats high E2 resulted in greater use of a place strategy (indicative of survey knowledge) than ovariectomized rats that received a lower dose of E2, who utilized more of a response strategy (indicative of route knowledge; Quinlan, Hussain, & Brake, 2008). However, it is noted in this same study that when a moderate dose of dopamine was administered, low E2 rats also shifted to place strategies, whereas high E2 rats maintained place strategy usage. This assumes lower estradiol alone does not imply impaired spatial knowledge, and estradiol may affect navigation strategies via dopaminergic motivational processes. Finally, there is direct evidence in rat studies that the hippocampus is an important modulatory area for E2 promoting place strategies, as direct infusions of E2 into

the dorsal hippocampus alone increased usage of place strategies, in contrast to direct E2 infusions in the dorsolateral striatum (Zurkovsky, Brown, & Korol, 2006).

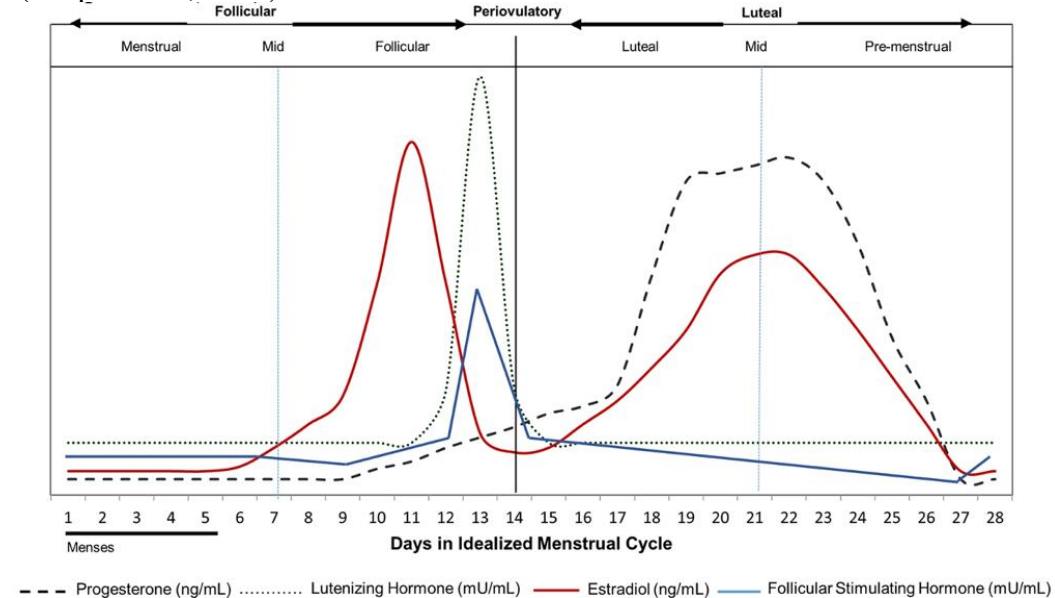
While E2 generally promotes the use of place-based strategies in rats, progesterone seems to have an inhibitory effect on survey knowledge acquisition. In a more recent study with ovariectomized female rats, it was found that while high E2 alone promoted the use of place-based strategies in a dual-solution T-maze, the administration of progesterone 1 or 4 hours before testing in the T-maze reversed this effect, biasing the rats towards using response strategies (Lacasse et al., 2022). To further complicate the role of ovarian hormones in female rats, progesterone may only produce inhibitory effects on the use of place strategies when E2 is present; this effect does not occur in ovariectomized rats when E2 is absent (Gomez-Perales & Brake, 2023). Taken together, these findings suggest that navigation strategy may be shaped by dynamic hormonal interactions, rather than the independent effects of a single hormone in naturalistic settings.

In summary, ovarian hormones play an important role in navigation strategy and behaviors in animal models. More specifically, estradiol generally has a positive impact on the use of place-based strategies, especially when used as a mechanism for spatial memory consolidation, when higher doses are administered, and when administering estradiol directly into the hippocampus of ovariectomized female rats. Progesterone, in contrast, has an inhibitory effect on place-based strategy use and instead increases response-based behaviors, but only in the presence of estradiol (meaning progesterone has interactive effects with estradiol, rather than an independent impact on navigation strategy).

Human Studies. The results in studies with humans, however, are not so cleanly apparent – possibly because there has been less work devoted to its study, lesion studies

cannot typically be conducted on humans to test direct impacts of ovarian hormones on spatial abilities, and humans may have more complex endocrine systems than rodents. The menstrual cycle in women is characterized by 3 broad stages over the course of roughly 28 days: the follicular phase, ovulation, and the luteal phase. The follicular phase begins on the first day of menses (or a period), and lasts until ovulation, for a total of roughly 14 days. Over the course of the follicular phase, estradiol and FSH rise, causing the uterine lining to grow and thicken, and follicles in the ovaries develop into an egg. During ovulation (a roughly one-day process), LH has a sharp increase, causing the ovary to release the developed egg. This then leads to a drastic decrease in LH, FSH, and estradiol. Finally, over the course of the luteal phase (days 15-28), progesterone and estradiol rise to prepare the uterine lining for possible pregnancy. If pregnancy does not occur, estradiol and progesterone start to decline to prepare for menses and the cycle begins again (see Figure 3, diagrammed by Draper et al., 2018).

Figure 3. Graphical Representation of Hormonal Fluctuations Across the Human Menstrual Cycle (Draper et al., 2018).



In women, Hampson (1990) found that cognitive skills differed depending on whether or not women were in the menstruation or midluteal phases of their cycles (i.e., short-term impacts of ovarian hormones) – spatial task performance (via pen-and-paper tasks, such as hidden figures, rod-and-frame, and spatial relations) was better in the early follicular/menstrual phase (i.e., when estradiol is low), and worse in the midluteal phase (i.e., when estradiol and progesterone are higher). In this same study, the opposite pattern was found for measures related to verbal-articulation, fine motor skills, verbal fluency, and perceptual speed (performance was better in the midluteal phase). From these findings, it was suggested that gonadal hormones (both estradiol and progesterone) improve abilities that typically favor females (such as articulation, fluency, and perceptual speed), and impair abilities that favor males (such as spatial abilities and abstract reasoning).

The vast majority of research studies examining spatial ability with the menstrual cycle uses mental rotation as a proxy for all spatial ability. Multiple studies have found that, in contrast to navigation in rodent studies, mental rotation performance in human women is

significantly higher in the early follicular (menses) phase than in the midluteal phase (Moody et al., 1997; Hausmann et al., 2000; McCormick & Teillon, 2001; Maki et al., 2002; Peragine et al., 2020; Hromatko & Tadinac, 2024 (for 3D mental rotation). Another study focused on examining estradiol, low estradiol similarly exhibited better mental rotation performance than high estradiol, (i.e., the early follicular phase outperformed both the ovulatory window and midluteal phases, which are both higher in estradiol) (Hampson et al., 2014). While some studies did not replicate this pattern of results (Schoning et al., 2007; Kozaki & Yasukouchi, 2009; Hromatko & Tadinac, 2024; Pletzer et al., 2024), it could in part be that the early follicular advantage is only present when it is a 3D mental rotation task, rather than 2D (Hromatko & Tadinac, 2024). These effects have also been examined in relations to sex differences between men and women in mental rotation abilities, with some finding that the male advantage in performance only existed when women were in the midluteal, but not the early follicular, phase (Moody, 1997; McCormick & Teillon, 2001; Schöning et al., 2007; Peragine et al., 2020), and a couple found this male advantage existed regardless of menstrual phase (Kozaki & Yasukouchi, 2009; Courvoisier et al., 2013).

Despite a relatively robust literature dedicated to mental rotation, there has been far less research examining the menstrual cycle with large-scale spatial ability (i.e., navigation). One study found that path integration – the ability to continuously update one’s position and orientation in space only from self-motion, especially proprioceptive and vestibular cues (Mittelstaedt & Mittelstaedt, 1982; Loomis et al., 1993) – differed by cycle phase, in that women in their ovulatory window had worse performance than women in their early follicular and midluteal phases (Brown et al., 2023). However, women in the ovulatory

window performed better when a landmark was present, suggesting that spatial ability is differentially associated with the menstrual cycle in women.

Most existing studies that do examine navigation with the menstrual cycle are primarily focused on navigation strategy (similar to rodent studies), specifically the use of place-based versus route/response-based strategies. One study found that women in their midluteal phase rely more on place-based strategies for solving an 8-arm radial maze than women in their early follicular and ovulatory phases (Hussain et al., 2016), whereas another study found that women in their midluteal phase relied more on response-based strategies when solving a 2D navigation task than when they were in their early follicular phase (Scheuringer & Pletzer, 2017). A follow-up study using the same type of 2D navigation task found that women in the ovulatory window used more place-based strategies than women in the early follicular or midluteal phases of their cycle (Bernal et al., 2020), and while a different study using the same task did not find any behavioral differences across cycle phases, they did find that the ovulatory window resulted in increased hippocampal activation during the task, whereas the midluteal phase resulted in decreased left hippocampal activity (Pletzer et al., 2019). In sum, the work surrounding the relationship between the menstrual cycle and large-scale navigation is sparse and lacks a clear pattern.

Endocrine Aging and Navigation Ability. Not only is spatial ability partially cycle-dependent in women, but endocrine aging plays a role as well (i.e., long-term impacts of ovarian hormones). It is around midlife (roughly ages 45 to 55) that women begin to experience natural menopause, which is characterized as the permanent absence of a menstrual cycle. A little before the menopausal transition, FSH begins to rise, as a consequence of declining levels in inhibin B levels, whereas estradiol levels remain relatively

similar. At onset of the menopausal transition, menstrual cycles become more irregular (this period is known as perimenopause), with FSH levels continuing to increase. Once a woman has experienced complete amenorrhea (or the absence of a menstrual cycle), they are considered as being postmenopausal. Postmenopausal women, along with having amenorrhea for 12 or more months, also have significantly low estradiol levels, with possibly lowered progesterone levels (Burger et al., 2007).

When examining the direct relationship between endocrine aging and navigation ability, a recent study found that midlife women in the perimenopausal stage showed greater use of response strategies in a desktop navigation task compared to midlife women in the premenopausal stage (Yu et al., 2023). While no differences were found in survey knowledge acquisition as measured by a pointing task and wayfinding efficiency (possibly due to a floor effect, as performance was barely above chance), there is indication that changes in navigation ability begin as early as midlife within the perimenopausal stage, and this may be due to endocrine aging. It was additionally found that hereditary and physiological Alzheimer's disease (AD) risk could be predicted by impaired path integration ability in midlife adults (Newton et al., 2023), shedding more light on the importance of studying the potential loss of navigation ability in midlife, rather than focusing solely on older adults.

Not only do women consist of nearly two-thirds of all late-onset AD cases, but the risk for developing Alzheimer's significantly increases in women during and after the menopausal transition (Mosconi et al., 2018), which occurs most commonly in midlife. Menopause also results in a decline in general cognitive ability in women (Marques Conde et al., 2021). Additionally, the age of onset of menopause may be a critical factor for cognitive

decline—earlier onset of menopause in women has been associated with greater cognitive decline over time compared to later onset of menopause (Koebele et al., 2017).

To further support the notion that estradiol may be important for navigation, women who receive bilateral salpingo-oophorectomies (i.e., the surgical removal of both ovaries and fallopian tubes) prior to menopause onset show more medial temporal lobe neurodegeneration than women who naturally experience menopause (Zeydan et al., 2019). Some interventions in women with endocrine disorders (e.g., endometriosis) involve menopause inductions (either through chemical castration or surgical removal of the uterus) when symptoms, such as chronic pain, are severe enough to not respond to alternative treatments (World Health Organization, 2025). As sex differences are apparent in hippocampal connectivity and neurodegeneration of the hippocampus (Yagi & Galea, 2019), and estradiol is important for memory consolidation in the hippocampus in women (Finney et al., 2020), it is important to continue to research the role of navigation ability and endocrine aging in women, especially in women that experience menopause at younger ages (as a treatment for endocrine conditions or otherwise).

Methodological Considerations

My studies used virtual environment technology to examine navigation ability. Given its high degree of experimental control, measuring spatial knowledge acquisition in virtual reality (VR) interfaces provides large benefits across a variety of populations. While measuring navigation in a real environment is the most directly translatable way to study spatial knowledge acquisition behaviors, it is wrought with many confounds such as prior familiarity of participants, weather, noise, and sun exposure, and cannot be administered reliably across different lab settings. These confounds become even more problematic in

cases where populations are being tested at multiple timepoints, as they would require multiple environments to minimize learning and familiarity effects.

Developing environments in virtual reality (VR) directly addresses a lot of the confounds present in measuring navigation in the real world, but many studies examining navigation differ in the interface used to interact with the environments. The easiest, most cost-effective option that can be used across most laboratories is desktop VR (Weisberg et al., 2014; Hejtmanek et al., 2018; Boone et al., 2018; van der Ham, 2020; Malanchini et al., 2020; Barhorst-Cates et al., 2021, Miola et al., 2021, Muffato et al., 2023; Topete et al., 2025; Lader et al., 2025), in which participants view the environment on a computer monitor and interact with the environment via keypresses, mouse, keyboard, or joystick. However, desktop interfaces do not allow for some potentially critical perceptual information navigation, such as proprioceptive-based cues and vestibular information as well as a restricted field of view.

To address these issues researchers have also administered navigation tasks in ambulatory, immersive VR (Chance et al., 1998; Klatzky et al., 1998; Waller et al., 1998; Loomis et al., 2001; Chrastil & Warren, 2013; He et al., 2023; De Back et al., 2025) in which people freely walk in the environment and therefore receive proprioceptive and vestibular information and also have a larger field of view. Even then, these environments are constrained in that they typically cannot exceed the size of a room space. Variability in how people interface with virtual environments, and the size constraints on ambulatory immersive environments raise questions of whether researchers are measuring the same abilities in virtual environments with different interfaces and sizes, and whether these factors affect learning and navigation in virtual environments. As the majority (if not all) of studies

examining ovarian hormones and spatial navigation in women have been previously conducted in desktop VR (e.g., Hussain et al., 2016; Scheuringer & Pletzer, 2017; Bernal et al., 2020; Patel et al., 2022; Brown et al., 2023; Yu et al., 2023; Joue et al., 2024), and Chapter IV was conducted in desktop VR due to timing and space constraints as part of a larger study, it is important to understand how desktop and immersive VR navigation are associated with each other.

Gaps in Current Literature

First, taking into consideration the methodological approaches for studying individual differences in navigation, there are few studies that directly examine how different virtual reality (VR) interfaces impact spatial knowledge acquisition in spatial learning tasks, especially in the inclusion of ambulatory environments. It has been proposed that body-based cues derived from locomotion are associated with greater acquisition of survey knowledge, but not graph knowledge (Chrastil & Warren, 2013; 2015). Given this, it is important to address the generalizability of using different VR environments in spatial learning to different outcome measures (specifically, the distinction between pointing and wayfinding).

While sex differences are pretty well-documented in the spatial navigation literature (Nazareth et al., 2019), the underpinnings of these differences, from an endocrine perspective, are not so well understood. In non-human mammal neuroscience research, there has historically been an extremely disproportionate bias towards using males over females (at a rate of more than 5 to 1), and many studies that have used both male and female mammals failed to distinguish by sex in their results (Beery & Zucker, 2011). While the National Institute of Health's (NIH's) initiative to make research more sex-inclusive since then has been successful (i.e., it increased the number of studies using female mammals), it did not

increase the proportion of studies that actually reported results by sex (Woitowich, Beery, & Woodruff, 2020). Based on these biases and lack of reported results, potentially valuable information on how sex plays a role in neuroscience and cognition is lacking— more specifically, in the domain of women’s cognitive abilities through an endocrine standpoint.

Regarding short-term changes in ovarian hormones (i.e., across the menstrual cycle) and their role in large-scale spatial learning, the literature is sparse and there is no clear pattern of effects in human research. As a large proportion of previous studies compare the early follicular with the midluteal phase of the menstrual cycle, it is possible that the main driver behind these mixed findings in women is the increase in progesterone that occurs in the midluteal phase, as progesterone, in addition to estrogen, has been seen to dynamically alter brain morphology across the menstrual cycle (Taylor et al., 2020). For studies that have found the midluteal phase is associated with worse performance, this could be due to progesterone having an inhibitory effect on navigation ability, as previously demonstrated in rat studies (Lacasse et al., 2022; Gomez-Perales & Brake, 2023). To date, no studies to our knowledge have assessed both ovarian hormones in women and navigation measures after learning in an immersive VR environment. In contrast, previous studies are limited to desktop measures (Hussain et al., 2016; Scheuringer & Pletzer, 2017; Pletzer et al., 2019; Bernal et al., 2020; Patel et al., 2022; Brown et al., 2023), and only a few included phases of the menstrual cycle that differ primarily in estradiol concentrations (e.g., Hussain et al., 2016; Pletzer et al., 2019; Bernal et al., 2020). In sum, the short-term impacts of ovarian hormones on spatial navigation abilities are still largely unknown, and have yet to be investigated in more naturalistic settings and at multiple points of the menstrual cycle.

Prior work that examines the role of endocrine aging and navigation ability (long-term changes in ovarian hormones), independent of natural cognitive decline due to aging, is either nonexistent or sparse. It is indeed possible that deficits in cognitive function that women experience during and after menopause are amplified by the aging process, and as a consequence the magnitude of endocrine aging effects is not well understood. As it has been seen that earlier onset of menopause demonstrates greater cognitive decline over time than a later onset of menopause (Koebele et al., 2017), it is important to distinguish the role of estradiol in navigation ability independently of aging. This can be examined in women with endometriosis (an estrogen-dependent, chronic inflammatory condition, Vercellini et al., 2014), who may opt to undergo some form of menopause (chemical or surgical) as a treatment for severe chronic pain, but to our knowledge this is the first study (along with other measures of general cognition) to investigate this question with respect to navigation ability.

The Present Studies

In this series of studies, the role of hormones (estradiol, and progesterone) in spatial navigation was examined in desktop and ambulatory immersive environments. These studies directly aimed to fill the gaps in literature noted in the above section.

Chapter II examines spatial knowledge acquisition in ambulatory immersive and desktop VR environments, across different environment scales (10 x 10m or 55 x 55m spaces). This is accomplished via two studies. The first study takes a within-subjects approach, examining participants' spatial knowledge acquisition (pointing and wayfinding) in both desktop and immersive environments to determine if performance in the two modalities are generally correlated with each other in identically-structured learning

experiences. The second study takes a between-subject approach, manipulating both interface and environment size in otherwise identically-structured environments to examine how these factors affect the ability to point and find one's way to objects previously learned in the environment.

In Chapters III and IV, the environment interface and scale differed between each other. Chapter III adopted an immersive VR environment that was small in scale (approximately 10 x 10m), whereas Chapter IV relied on using a desktop, larger-scale (55 x 55m) environment as it was included in the context of a larger study¹. To address this procedural difference, Chapter II focuses on measuring spatial knowledge acquisition in different VR interfaces (immersive ambulatory or desktop), environment scales (10 x 10m or 55 x 55m) and measures of spatial knowledge types (pointing and wayfinding) to examine the extent to which learning in these interfaces measures the same or different abilities, necessary to relate the results of the studies in Chapter III and IV.

Chapter III examines the role of the menstrual cycle phase in immersive VR navigation. Women's navigation abilities are measured in different phases of the menstrual cycle, to assess any potential differences in navigation ability between when estradiol is high (i.e., the ovulatory window) and low (i.e., in the early follicular phase/menses). Additionally, women were tested on an aspect of small-scale spatial cognition ability, a mental rotation task, as well as several other tasks of general cognitive function (including processing speed, inhibition, executive function, working memory, and episodic memory) to determine if cycle phase effects are limited to spatial abilities, or if estradiol has a global impact on general cognitive abilities.

¹ Participants were studied in Santa Barbara and San Diego, and could only reliably be run in a cubicle setting across both sites.

Chapter IV dives more specifically into the role of estradiol in spatial navigation, by examining the effects of chemically-induced ovarian hormone suppression in young adult women. This study takes a between-subjects longitudinal approach, by testing *Cases* (women before and after chemically-induced menopause), and relatively age-matched *Controls* (naturally cycling or progestin-only contraceptive user women) on their navigation ability over the course of three months. Additionally, we included another measure of hippocampal function (a face-name associative memory exam, assumed to be a measure of episodic memory) to determine if general hippocampal-based tasks are impacted by ovarian hormone suppression over time.

II. Comparing Navigation Ability in Desktop and Ambulatory Immersive Virtual Environments

In a world where people are constantly traveling between places to get to work, school, home, and so forth, the ability to successfully navigate and remember the layouts of environments is crucial. Research on *how* humans acquire spatial knowledge of their environments has expanded in the last few decades due to the availability and development of virtual technologies to build controlled environments. The use of Virtual Reality (VR) provides large benefits for studying navigation. While measuring navigation in real environments is the most directly translatable way to study spatial knowledge acquisition behaviors, it is wrought with many confounds such as prior familiarity of participants, weather, noise, and sun exposure, and cannot be administered reliably across multiple lab settings. Developing environments in VR allows full experimental control, can be used to create ecologically valid measures that can be used across many labs (Loomis et al., 1999), and can be easily administered in smaller lab spaces.

Given its high degree of experimental control, using VR has become the standard in spatial navigation research. Researchers have developed VR environments representing college campuses (Weisberg & Newcombe, 2014), museums (Cao et al., 2019), indoor mazes (Marchette et al., 2011; Boone et al., 2018), multi-floor office buildings (Richardson et al., 1999), water mazes (Clemenson & Stark, 2015; de Castell, 2019), towns and cities (Miola et al., 2021; Tansan, et al., 2025), hedge mazes (Chrastil & Warren, 2013), and natural environments like deserts, savannahs, and forests (Padilla et al., 2017; Gagnon et al., 2018, Barhorst-Cates et al., 2021). These environments differ in numerous aspects, including size (and therefore the distance required to travel in the environment), number of turns, path regularity (e.g., straight paths with 90 degree turns versus irregular paths with a wide range

of turning angles), and can be manipulated in different experimental conditions, for example, to vary the visibility of distal landmarks (e.g., mountains, the sun, or large objects such as skyscrapers or a distinctive tree).

Existing VR environments also differ in the interface used to interact with the environments. The easiest, most cost-effective option that can be used across most laboratories is desktop VR (Weisberg et al., 2014; Hejtmanek et al., 2018; Boone et al., 2018; van der Ham, 2020; Malanchini et al., 2020; Barhorst-Cates et al., 2021, Miola et al., 2021, Muffato et al., 2023; Topete et al., 2025; Lader et al., 2025). In these environments, participants view the environment via a computer monitor, and interact with or move through the environment via a series of keypresses, mouse, keyboard, or joystick. However, desktop interfaces do not allow for some potentially critical perceptual information navigation, such as proprioceptive-based cues and vestibular information cues that are ascertained from being able to physically locomote in a space, as well as restricting the field of view.

To address these issues researchers have also administered navigation tasks in ambulatory, immersive VR (Chance et al., 1998; Klatzky et al., 1998; Waller et al., 1998; Loomis et al., 2001; Chrastil & Warren, 2013; He et al., 2023 De Back et al., 2025) in which people freely walk in the environment and therefore receive proprioceptive and vestibular information and also have a larger field of view. This is a less common approach as researchers require a space large enough to allow for participants to walk freely through the simulated environment. Even then, these environments are constrained in that they typically cannot exceed the size of a room space. More recently, researchers have attempted to increase environment size by administering tasks using immersive VR and treadmills (Ruddle et al., 2011; Starrett et al., 2019; Hejtmanek et al., 2020; Li et al., 2021; Zhou et al.,

2025), but this method is not ideal as more readily available omnidirectional treadmills require somewhat less naturalistic movements (e.g., sliding feet on a platform) to travel through the environment (Lewis et al., 2024).

Variability in how people interface with virtual environments, and the size constraints on ambulatory immersive environments raise questions of whether researchers are measuring the same abilities in virtual environments with different interfaces and sizes and whether these factors affect learning and navigation in virtual environments. People can acquire different types of spatial knowledge from navigation experience. Historically, the primary distinction is between landmark knowledge, route knowledge, and survey knowledge (Siegel & White, 1975; Montello, 1998) which differ in the representational information about an environment. Landmark knowledge consists of knowing and recognizing the landmarks within a given environment. Route knowledge is the ability to remember the specific routes previously traveled when learning a specific environment, typically via an egocentric perspective (i.e., thinking about directions relative to the self, such as left and right). Survey knowledge includes knowledge of metric distances and angular directions between locations and landmarks, and is knowledge that can be derived independently of a previously learned path, and is what researchers tend to equate with as the ability to construct a “cognitive map,” or a more holistic, internal representation of an environment (Tolman, 1948). Some navigation tasks can also be accomplished using graph knowledge, which is intermediate between route and survey knowledge (Kuipers, 2000; Chrastil & Warren, 2015). Graph knowledge consists of topological path relations between locations and landmarks in an environment beyond the originally experienced paths (like survey knowledge), but, unlike survey knowledge, does not contain (or contains vague/little) metric information about

distances or directions. It is to be noted, however, that measures of graph knowledge may be more reflective of survey knowledge that requires less precision to be successful, and may reflect more of a continuum, rather than separation, of ability.

These types of knowledge can be measured by different tasks. For example, landmark knowledge can be assessed via a landmark recognition task (such as labeling landmarks, listing them out, or recognizing landmarks encountered in an environment). Route knowledge is typically assessed via a route retracing task, especially when people learn the environment by following a guided route (or series of guided routes). Survey knowledge can be assessed via tasks such as reconstructing a map of an environment, pointing to landmarks from different locations within the environment (onsite pointing) or imagining being in the environment at a specific place and facing direction and pointing to other landmarks (offsite pointing or judgments of relative direction) imagining straight line directions and pointing to landmarks. While efficient wayfinding can reflect either graph or survey knowledge acquisition (and it is debated whether these are separate abilities to begin with), these have been dissociated in studies that examined navigation in different types of environments including non-Euclidean spaces (Warren et al., 2017; Murry & Glennerster, 2021; Peer et al., 2024).

Some studies have attempted to examine differences in navigation ability in real and virtual environments with different interfaces. For example, Richardson and colleagues (1999) found that while people can reliably acquire spatial knowledge of environments in desktop VR, the ability to point and reconstruct a map of the learned environment was better when the environment was learned in the real-world, and attributed this difference primarily to being able to physically locomote in the real environment. Differences in knowledge

acquisition between VR interfaces has shown more mixed results, but several studies have found that when immersive VR included physical locomotion, participants acquire more spatial knowledge than in desktop interfaces (Anastasiou et al., 2023; De Back et al., 2025), and one study found that learning an environment in ambulatory immersive VR resulted in similar performance to learning in the real world (Li et al., 2021). Moreover, when participants used a controller to navigate through an environment (without physically walking or turning), there was little to no advantage to using immersive over desktop VR (Ruddle & Peruch, 2004; Li & Guidice, 2013; Zhao et al., 2020; Feng et al., 2022; Thorp et al., 2024).

However, this advantage in immersive VR on performance has been interpreted as a boost to specifically survey knowledge metrics. Chrastil and Warren (2013) found that onsite pointing ability was better after learning in immersive VR, than after learning in a desktop VR condition. The authors argued that the ability to point to unseen objects was a survey knowledge metric, and the inclusion of body-based cues when learning an environment boosts survey knowledge acquisition. In contrast, a follow-up study found that the ability to find one's way to objects did not significantly differ between immersive and desktop VR, proposing that wayfinding was a measure of graph knowledge, and does not rely on the inclusion of body-based cues for successful performance (Chrastil & Warren, 2015).

A small body of work has directly examined the effects of environment size on spatial knowledge on measure spatial knowledge acquisition and navigation. Ruddle and colleagues (2011) examined navigation ability in marketplace environments that were either large (65 x 45m) or small (9.75 x 6.75m) in extent, and found that locomotion and bodily rotations in immersive VR (compared to visual only movement or joystick-based rotation) improved

navigation performance in smaller environments, while walking (but not body rotations alone) were associated with better navigation in large environments. Additionally, Topete and colleagues (2025) examined learning and navigation in desktop VR simulations of a relatively large, open irregular outdoor campus and a smaller gridlike maze and found that navigation performance was partially dependent on the type of environment learned, such that abilities measured in the larger environment were partially dissociated from abilities measured in the smaller environment, but the abilities were highly correlated). Similarly, Lader and colleagues (2025) found separable factors/abilities associated with learning the layout of a large open campus in desktop VR, a gridded town in desktop VR, and a gridded real-world environment, but the factors were highly correlated.

On the basis of this review of previous studies we can identify gaps in our understanding of factors that affect the measurement of navigation ability. First, previous work comparing navigation in immersive and desktop VR interfaces primarily depended on tasks designed to measure cognitive map formation (i.e., survey knowledge) such as direction or distance estimates (which require metric information), or the ability to reconstruct a map of the environment. Less work has examined both a survey knowledge metric (such as pointing) and wayfinding ability, which might be accomplished with graph knowledge, in the same study, which could potentially distinguish between factors that enable the acquisition of graph versus survey knowledge. Previous studies that measured both pointing and wayfinding (the ability to navigate between objects in an environment) found that they were very highly correlated and did not define separate factors (Topete et al., 2025; He et al., 2023; Zhou et al., 2026), but these findings may, in part, be due to the researchers only

examining these measures in one interface (desktop VR, immersive VR, and real-world only, respectively).

Another gap in our knowledge is that it is unclear how much learning in desktop and immersive VR measures the same abilities because some existing studies (e.g., Ruddle et al., 2011) manipulated the type of virtual environment between, rather than within subjects. Some studies (e.g., Topete et al., 2025; Lader et al., 2025) measured learning in different environments by the same participants, enabling correlational analyses, but in these studies the environments differed in many ways (e.g., gridlike vs. irregular paths, indoor vs. outdoor, presence of distal cues in some environments, different learning experiences). Therefore, it is not possible to determine if the separable factors were due to environment size or other aspects in which they differed.

Finally, it is possible that some of the differences between desktop and immersive virtual environments are due to motion sickness (i.e., cybersickness). Motion sickness is expected to occur due to the sensory conflict between visual, vestibular, and proprioceptive cues (McCauley & Sharkey, 1992), which has been shown to occur in desktop VR, as well as immersive VR when naturalistic walking was not available (Mayor et al., 2021) or when head movement is restricted (Luong et al., 2022). While some studies found that immersive VR contributed to greater motion sickness rates than desktop VR (e.g., Martirosov et al., 2021; Eudave & Martinez, 2025), this could be due to the fact that each of these studies participants did not walk in the immersive environment. In sum, it is likely that immersive VR contributes to greater motion sickness only when naturalistic walking is not available, and may be lessened when the experience is more naturalistic.

The present studies attempt to bridge the gaps in previous literature by manipulating the interface and size of the environment learned, but controlling for the learning experience, structure of the environment, and relative landmark locations. Study 1 measures spatial layout learning in immersive and desktop VR interfaces in a within-subjects design to assess if learning in the two interfaces is correlated. Study 2 uses a between-subjects approach to measure navigation ability in the same environment, but manipulating both the interface (immersive or desktop VR) and environment size (10 x 10m or 55 x 55m space). Additionally, both studies include measures to assess both survey and graph knowledge via a pointing task and a wayfinding task (respectively), and examine the extent to which motion sickness can account for differences in performance across interfaces.

The first hypothesis is that, navigation ability measured by pointing in immersive vs. desktop VR and wayfinding in immersive vs. desktop VR will be highly correlated with each other. The second hypothesis is that participants will exhibit better pointing performance in immersive VR than in desktop interfaces due to the inclusion of body-based proprioceptive and vestibular cues (e.g., Ruddle et al., 2011; Anastasiou et al., 2023, De Back et al., 2025) and a wider field of view. Regarding wayfinding, we examine 2 alternative hypotheses. The first is that if successful wayfinding relies only on graph knowledge, which is proposed to not rely on locomotion and vestibular cues during spatial learning, there should be no differences in performance between immersive and desktop interfaces (Chrastil & Warren, 2013; 2015). The second is that if successful wayfinding is aided by survey knowledge which is enhanced by body-based cues during learning, and more related to pointing ability, performance will be significantly better in immersive VR than in desktop VR (He et al., 2023; Topete et al., 2025; Zhou et al., 2026). Finally, we hypothesized that desktop VR would have higher self-reported

rates of motion sickness than ambulatory immersive due to increased sensory conflict in the desktop condition (McCauley & Sharkey, 1992; Mayor et al., 2021) and explored whether differences in motion sickness accounted for any differences in performance between desktop and immersive VR.

Study 1: Immersive Ambulatory and Desktop Navigation (Within-Subjects)

1.1 Method

1.1.1 Participants

Participants were undergraduate students recruited from the institution's participant pool, with 45 originally recruited to participate. Four were removed due to technical failures, and three dropped out due to motion sickness. The final dataset of 38 participants ranged from ages 18-32 ($M = 19.9$ years, $SD = 2.5$ years), and comprised 21 women and 17 men. Participants either received course credit (2 hours) or payment (\$30) in exchange for their time.

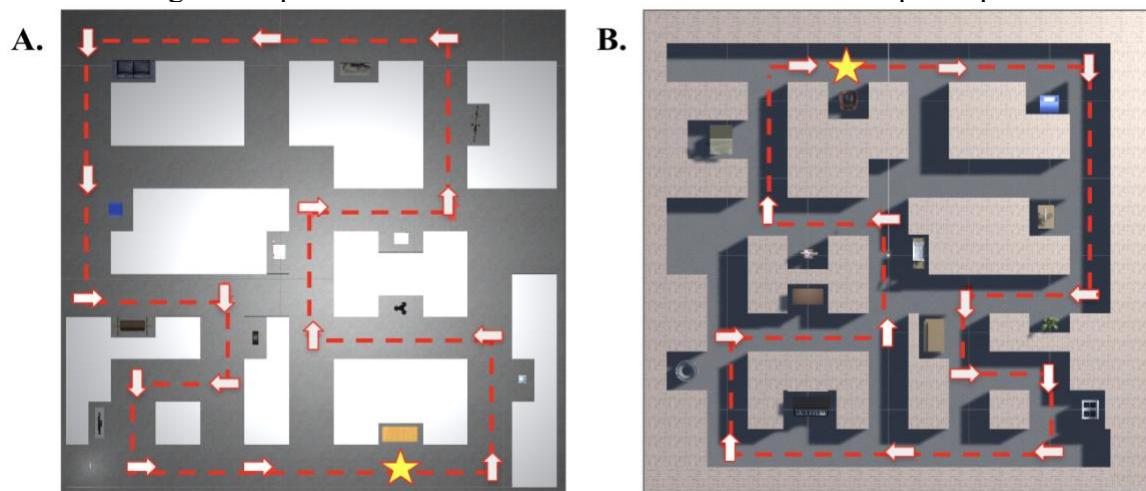
1.1.2 Materials

Desktop Navigation Ability. The desktop maze task (updated from Boone et al., 2018, see Figures 3A and 4A-C) was administered to measure navigation ability in a desktop interface. Participants completed all tasks via a desktop monitor, keyboard, and mouse. In the learning phase, participants follow a single, guided route indicated by red arrows on the ground that expose them to 12 objects and task them with remembering the locations of these objects. This version of the maze is composed of solid grey walls and contains the following objects: TV, bicycle, desk, statue, clock, swing, stepladder, fridge, water cooler, streetlamp, couch, and phonebooth. This desktop environment is conducted in a 55 x 55m virtual space, and viewed on a desktop monitor.

The onsite pointing task consists of 20 trials, in which participants are placed in front of some starting object and use the mouse to turn and “Enter” key to point to the estimated direction of a target object. Pointing ability is calculated as the average absolute angular error across the 20 trials, which is the deviation between a participant’s estimated angular location of a target object and its actual angular location. Scores range from 0-180 degrees, where higher values indicate worse performance.

The wayfinding task follows a similar format as the pointing task, except participants are instructed to find (walk to) some target object using the WASD or arrow keys. Wayfinding efficiency is calculated as the excess distance traveled, or the difference between the actual distance a participant traveled subtracting the shortest possible distance, divided by the shortest possible distance. In this measure, higher scores indicate worse performance (whereas a score of 0 would indicate that the participant perfectly executed the shortest possible route in each trial).

Figure 3. Aerial views of the grey wall (A) and red brick (B) maze environments, with starting points and learning paths indicated. Both environments follow the same relative layout and structure (but are mirror-images of each other), with objects and environment textures changed to represent themselves as different environments to participants.



Immersive Ambulatory Navigation Ability. A modified, ambulatory immersive VR version of the grey wall maze (called the red-brick maze see Figures 3B and 4D-F), was developed from its original desktop version (Boone et al., 2018) and scaled down to approximately 10 x 10m to fit into the room space. While the red-brick version of the maze follows the same procedure and respective layout and object locations as the grey wall maze, the environment layouts are mirror images of each other to be perceived as novel environments. Additionally, this maze environment differs in that the walls are composed of red brick, and the environment contains different objects: chair, mailbox, plant, telescope, picnic table, stove/oven, piano, trash can, bookshelf, wheelbarrow, harp, and well. In this task, participants wore a wireless HTC VIVE Pro Eye head-mounted display (HMD) to walk through the environment and look around, and a controller to move between stages and complete trials. For the pointing trials, they used the controller to start trials and lock their facing position, and turned their body and head in place to face the perceived indicated direction of a target object (using the HMD to record orientation). For wayfinding, they used the controller to begin a trial, and physically walked in the environment using the HMD to locate target objects.

Figure 4. Screenshots of each task for the 55 x 55m grey wall (A-C) and 10 x 10m red brick (D-F) environments.

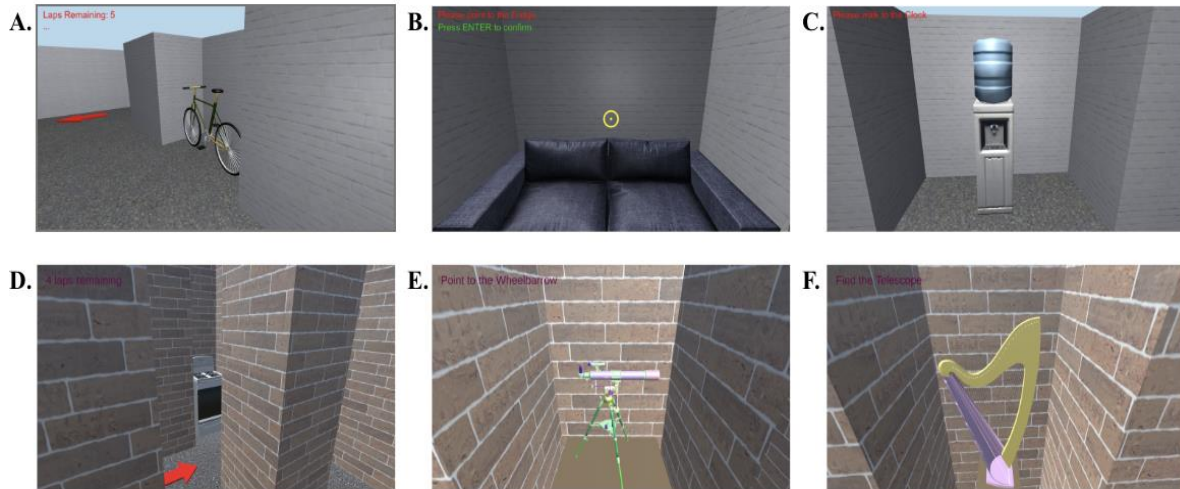


Figure 4A-C: Screenshots of the learning (A), pointing (B), and wayfinding (C) phases in the grey wall maze environment. Figure 4D-F: Screenshots of the learning (D), pointing (E), and wayfinding (F) phases in the red brick maze environment.

Environment Interface Experience. Six questions were administered to assess participants' experience in each virtual environment. Each question assessed a participant's level of stress when completing each navigation task, how much pressure they felt to do well, how motivated they felt to do well, and how much motion sickness they experienced in each interface on a scale of 1 to 5. The individual questions are described in Appendix A.

Other Measures. Additional measures were included in this study, including self-reported sense of direction (Hegarty et al., 2002), spatial anxiety (He & Hegarty, 2020), exploration tendency (He & Hegarty, 2020), navigational growth mindset (He & Hegarty, 2020), video game experience, GPS dependency (He & Hegarty, 2020), GPS usage (Topete et al., 2024), 4 saliva samples collected to measure basal and reactive cortisol concentrations (as part of a separate study examining the relationship between cortisol and non-stressful navigation), as well as a general grid task for general spatial memory.

1.1.3 Procedure

The Institutional Review Board (IRB) reviewed this study and approved it prior to the collection of any data (protocol #46-25-0194). Participants came into the lab space to complete the informed consent process in Qualtrics, and then were either walked to the immersive VR room (if they completed the immersive environment first) or stayed in the room where they provided consent (if they completed the desktop environment first). Participants were counterbalanced in the order that they completed the immersive and desktop VR tasks. Prior to beginning each navigation task, participants collected a first saliva sample.

For the immersive environment, participants were fitted with the HMD and controller, and placed into an empty environment. Upon receiving instructions for the learning phase, participants were placed into the starting point of the environment (after walking to a red starting point and pressing the trigger, originally starting at the chair) and began the learning phase. For the first lap participants were required to name the objects aloud to an experimenter (and were corrected by an experimenter if the object name was incorrect), but were otherwise not timed and could move at their own pace, given that they did not move backwards in the environment.

Once all 5 laps concluded, the environment faded and participants were instructed to begin the pointing phase. Participants were placed in front of a starting object in the environment, and told to rotate their bodies and head, using the HMD to face the perceived direction to a target object. They then pressed the controller when they believed they were facing the target object. The participants then completed the 20 onsite pointing trials in a randomized order, with the environment fading in between each trial to allow participants to walk to the next starting point without receiving other environmental cues. Participants were

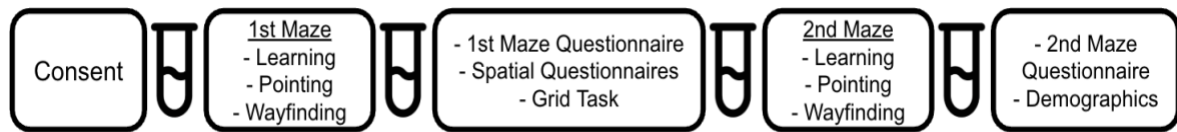
not timed in the onsite pointing task. Upon completion of the pointing phase, participants were given instructions and then began the 20 wayfinding trials in a random order. Each trial started in a similar fashion as the pointing task, in that participants were first placed in front of some starting object in the environment. In this phase, participants were given 45 seconds in each trial to walk to and find the target object, and when the participant either found the target or timed out, the environment faded in between trials to allow them to walk to the next starting point.

The desktop environment task followed the same experimental protocol as the immersive environment (learning, pointing, wayfinding), except using a computer monitor, keyboard, and mouse for movement and actions in the environment. More specifically, the keyboard was used for movement in the environment and moving between stages/trials, the mouse was used to rotate, turn, and indicate directions to target objects, and the monitor was used to view the environment. Additionally, the trials in the pointing and wayfinding phases automatically teleported participants to their next start location.

After completing all tasks in the immersive or desktop environment, another saliva sample was collected by participants. Then participants were brought back to the lab (if previously in the immersive VR room) and redirected back to the Qualtrics link to complete the questionnaires (see Figure 5 for a graphical representation of the procedure). First, they responded to their experience in the VR environment, and then were directed to complete the self-report surveys (SBSOD, Spatial Anxiety, Exploration Tendency, Navigational Growth Mindset, GPS Dependency, GPS Use, Video Game Experience). With the exception of the GPS Dependency scale always being completed immediately prior to the GPS Usage scale, all the self-report measures were randomized in their presentation order. Once participants

were finished with the self-report measures, they completed a grid task, then the next environment tasks (immersive or desktop), as well as providing saliva samples before and after the second environment. Finally, participants completed the final 6 questions asking about their experience in the environment, and responded to demographic questions (wake time, steroid use, age, sex, race, ethnicity) before concluding the study and being thanked for their time.

Figure 5. Procedure Outline for Study 1.



1.2 Results

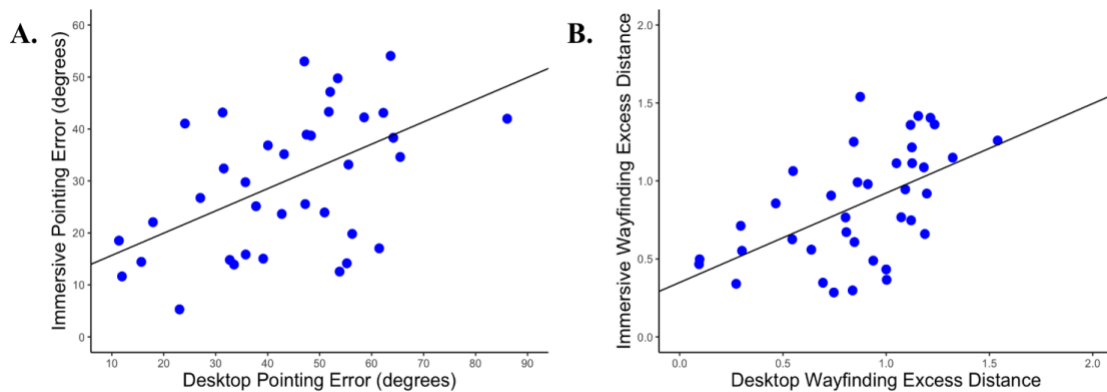
Descriptive statistics for onsite pointing and wayfinding excess distance are reported in Table 1, and Pearson's correlations were conducted to examine the associations in performance between the two interfaces. As noted in the table, the spatial learning variables did not depart from normality, and were demonstrated as reliable tasks.

Table 1. Descriptive Statistics for the Immersive and Desktop Navigation Outcome Tasks and Self-Report Measures (Study 1)

Variable	<i>M</i>	<i>SD</i>	Skew	Kurtosis	Omega
Immersive Onsite Pointing Error	30.46	14.00	0.17	-1.06	0.86
Immersive Wayfinding Excess Distance	0.85	0.36	0.14	-1.21	0.86
Desktop Onsite Pointing Error	44.51	17.39	0.01	-0.45	0.88
Desktop Wayfinding Excess Distance	0.87	0.35	-0.58	-0.36	0.67

We hypothesized that performance in the two versions of the task (immersive ambulatory and desktop VR) would be significantly positively correlated. Onsite pointing performance was significantly positively correlated in immersive and desktop VR, $r(36) = 0.53, p < .001$, as was wayfinding excess distance, $r(36) = 0.55, p < .001$ (see Figure 6). In sum, our first hypothesis was supported.

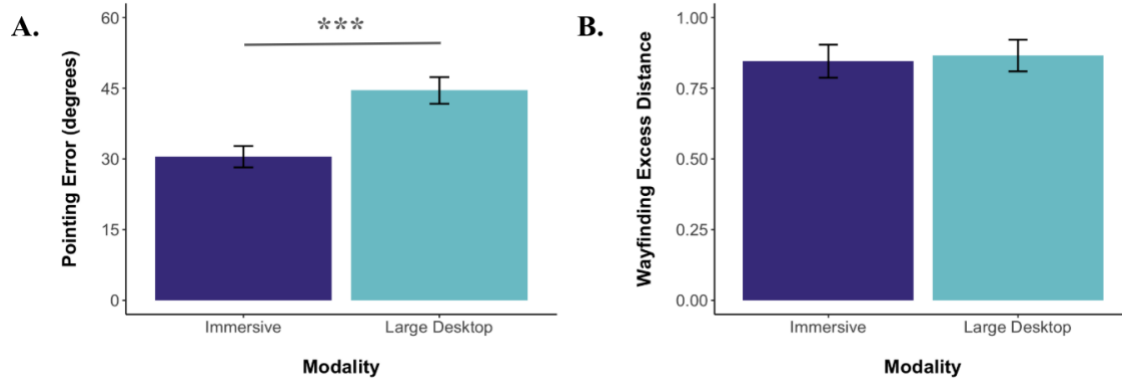
Figure 6. Study 1 Regression Plots for Immersive vs. Desktop Pointing Error (A) and Wayfinding Excess Distance (B).



We hypothesized that performance in the immersive virtual environment would be better than in the desktop virtual environment due to the availability of body-based cues in immersive VR (and not in desktop VR). To test this hypothesis, we conducted one-tailed paired samples t-tests between immersive and desktop onsite pointing and wayfinding excess distance. Onsite pointing in the immersive condition resulted in significantly lower angular error than the desktop condition, $t(37) = -5.60, p < .001, d = -0.91$ (see Figure 7A). In contrast, wayfinding excess distance was not significantly different between the two conditions, $t(37) = -0.37, p = .715, d = -0.06$ (see Figure 7B). Our second hypothesis was supported for onsite pointing, where performance was better in immersive VR with a large effect size. For wayfinding, we found no significant difference in performance between

interfaces (and a small effect size), supporting the alternative hypothesis that wayfinding would not differ between interfaces as it is a measure of graph knowledge acquisition.

Figure 7. Study 1 Bar Plots for Average Immersive and Desktop Pointing (A) and Wayfinding (B) Performance (N = 38), with Standard Errors.



Note: *** $p < .001$.

Finally, we hypothesized that motion sickness would be greater in the desktop condition due to the conflict between vestibular input and optic flow information while navigating. A one-tailed, paired samples t-test revealed that reported motion sickness was greater in the desktop condition ($M = 2.26$, $SD = 1.50$) than in the immersive condition ($M = 1.84$, $SD = 0.97$), $t(37) = 1.69$, $p = .05$, supporting the hypothesis. Since motion sickness was higher in the desktop condition, we included motion sickness as a covariate in ANCOVA analyses examining spatial learning performance (onsite pointing, wayfinding efficiency) by interface to determine if differences (or lack thereof) in performance was due to motion sickness impacting spatial learning. For onsite pointing, the ANCOVA revealed that while motion sickness significantly worsened pointing performance, $F(1,72) = 14.19$, $p < .001$, immersive VR pointing was still significantly better than desktop pointing ability after including motion sickness as a covariate, $F(1,72) = 12.44$, $p = .001$. For wayfinding efficiency, we found no significant effects of motion sickness ($p = .091$), nor interface ($p =$

.972). In sum, we found that while motion sickness was worse in the desktop condition, it did not impact previous results.

1.3 Discussion

In Study 1, we found that navigation performance in immersive and desktop VR interfaces was related – those who performed well in immersive also performed well in desktop VR, and vice versa. Additionally, while onsite pointing performance was better in ambulatory immersive VR than in desktop VR, wayfinding was not significantly different between the two interfaces. These findings are in line with proposed differences between survey and graph knowledge acquisition, as locomotion has been theorized to improve survey knowledge measures (such as pointing), but is not necessary for graph knowledge measures (such as wayfinding, Chrastil & Warren, 2013; 2015). Finally, we found that the desktop condition did result in higher motion sickness rates than the immersive condition, likely due to sensory conflict in the desktop condition and the incorporation of more naturalistic walking in the immersive condition (McCauley & Sharkey, 1992; Mayor et al., 2021).

In interpreting these findings, it is important to acknowledge confounds in this study. First, the two environments, despite having the same basic structure and layouts that were mirror images of each other, were developed to be *perceived* as different environments to attempt to minimize carry-over effects. The environments differed in their wall texture (red brick vs. grey wall) and objects, which could have contributed to performance differences. Critically, the environments differed not only in interface and appearance, but also scale. The immersive maze was scaled down from the original 55x55m environment to fit in a 10x10m room space, and therefore was more than 5 times smaller than the desktop maze.

Study 2 accounts for the confounds present in Study 1 by examining whether the differences in navigation performance are due to being administered in different interfaces, having different environmental scales, or if both interface and scale affect learning. In this study, we first hypothesized that we would replicate results from Study 1, in that pointing error would be lower (i.e., better) in immersive ambulatory VR than desktop VR. We expected no differences between conditions for wayfinding as found in Study 1, consistent with Chrastil and Warren (2013; 2015) that this measure relies more on graph knowledge and therefore does not require locomotion for knowledge acquisition. For hypotheses novel to Study 2, we predicted that if environment size does matter, then smaller environments would result in better overall navigation performance than larger environments, potentially due to the increased distance required to travel through them (Proffitt, 2006; Witt, 2011). If environment size does not matter, then we will not expect the conditions to significantly differ from each other in an environment that is otherwise identical.

Study 2: Navigation Ability in Different Interfaces and Scales (Between-Subjects)

2.1 Method

2.1.1 Participants

Participants were undergraduate students from the institution's participant pool, with 96 originally recruited to participate. Of these participants, one dropped out due to motion sickness during the navigation task, 1 was removed due to experimenter error, and 4 were removed due to technical errors. A final sample of 90 participants (30N in each maze condition) was analyzed, ranging from ages 18-39 ($M = 19.4$ years, $SD = 2.8$ years), and composed of 52 women, 36 men, 1 non-binary, and 1 who declined to state. Participants received either course credit (1-1.5 hours) or payment (\$15) for their time.

2.1.2 Materials

The following materials were administered in this study. Similar to Study 1, experimenters collected two saliva samples from the participants for cortisol assays (for one environment) as part of a separate study examining cortisol and navigation in non-stressful learning environments that will be reported elsewhere. Additionally, they completed the same self-report questionnaires as Study 1, with the exception that the video game questionnaire was expanded on, and the grid task was not included due to timing constraints.

Navigation Ability. In Study 2, the red-brick maze environment (Figures 3A and 4D-F) was used for each experimental condition. The large desktop reality maze (LDR) environment was based on the original task developed by Boone and colleagues (2018, 55 x 55m), but updated to be more user-friendly and decrease motion sickness via slowing down the movement speed and instructing experimenters to more closely monitor participants for signs of motion sickness. The small desktop reality environment (SDR) environment was only modified from the LDR environment in that the environment and objects were scaled down to fit in a 10x10m space. The ambulatory immersive VR (iVR) environment followed the same layout and size as the SDR environment, but was administered using an HMD and controller in a 10 x 10m room (and was the same environment administered in the immersive VR in Study 1). The tasks for each condition were identical to that described in Study 1 (learning, onsite pointing, wayfinding).

2.1.3 Procedure

The institution's IRB reviewed and approved this study prior to the collection of any data (protocol #46-25-0194). Participants were randomly assigned to conditions prior to participation, and either met an experimenter in the lab space (if in a desktop condition) or in

the VR lab (if in the immersive condition) and completed the informed consent process. The procedure for Study 2 followed the same sequence of events as Study 1, except participants only participated in one version of the environment (and thus only had 2 saliva samples collected and either completed the task in immersive ambulatory OR desktop VR).

2.2 Results

We hypothesized that pointing performance in the iVR condition would be better than both desktop conditions (SDR and LDR), but wayfinding excess distance would not significantly differ among conditions. We also examined whether environment size (in otherwise identical interfaces) resulted in differing navigation performance. To test these hypotheses, we conducted one-way between-subjects ANOVAs on onsite pointing ability and wayfinding excess distance between the iVR, LDR, and SDR conditions followed by post-hoc tests using Tukey's HSD.

Descriptive statistics for onsite pointing and wayfinding excess distance are presented in Table 2. As in Study 1, none of the variables departed from normality and were considered reliable measures. For onsite pointing, there was a significant main effect of condition, $F(2,87) = 13.09, p < .001, \eta^2 = .23$. Post-hoc testing using Tukey's HSD revealed that iVR pointing was better than both the LDR condition, $p < .001$, and the SDR condition, $p = .008$. However, there were no significant differences in pointing between the LDR and SDR conditions, $p = .116$ (see Figure 8A). In sum, we replicated Study 1 in that iVR resulted in better performance than both desktop conditions, and this effect was independent of environment size (as the desktop conditions did not significantly differ from each other).

Table 2. Descriptive Statistics for the Immersive and Desktop Navigation Outcome Measures (Study 2)

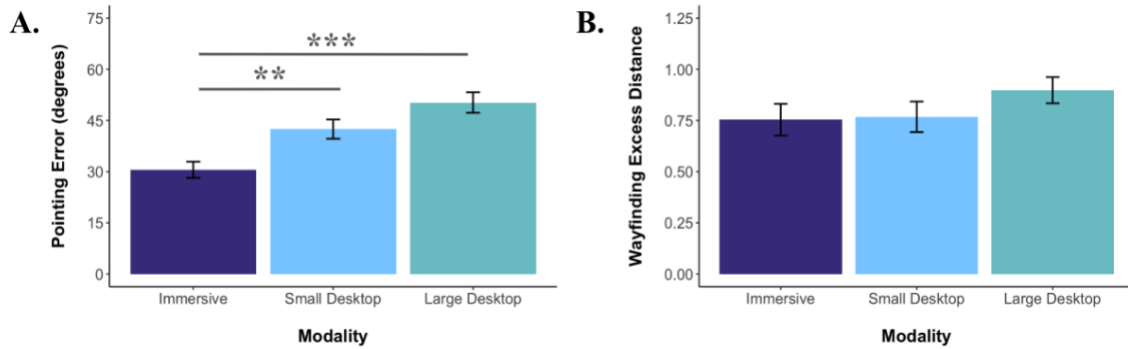
Variable	<i>M</i>	<i>SD</i>	Skew	Kurtosis	Omega
iVR Onsite Pointing Error	30.55	12.99	0.13	-1.16	0.70
iVR Wayfinding Excess Distance	0.75	0.42	0.72	-0.46	0.89
LDR Onsite Pointing Error	50.26	16.49	0.11	1.14	0.75
LDR Wayfinding Excess Distance	0.90	0.35	0.08	0.51	0.82
SDR Onsite Pointing Error	42.47	15.40	0.15	-0.28	0.83
SDR Wayfinding Excess Distance	0.77	0.41	0.50	-0.03	0.89

iVR = Immersive Ambulatory condition; LDR = Large Desktop condition, SDR = Small Desktop condition.

Note: Onsite pointing and wayfinding are measures of angular error (pointing) and excess distance (wayfinding), so higher scores indicate worse performance.

For wayfinding excess distance, there was no significant main effect of condition, $F(2, 87) = 1.21, p = .304, \eta^2 = .03$ (see Figure 8B). For wayfinding excess distance, we replicated Study 1 in that interface did not significantly contribute to any differences in performance. Novel findings reveal that environment size also did not contribute to any significant differences in wayfinding, in an otherwise identical environment.

Figure 8. Study 2 Bar Plots for Average iVR, SDR, and LDR Pointing (A) and Wayfinding (B) Performance (N = 30 in each condition), with Standard Errors.



Note: ** $p < .01$, *** $p < .001$.

In sum, our first hypothesis was supported – while iVR had better pointing performance than both desktop conditions, wayfinding excess distance was not significantly different between any conditions. Additionally, we found no evidence that environment size, in an otherwise identical maze-like environment, impacted navigation performance.

As in Study 1, we examined potential differences in motion sickness between conditions, to test the primary hypothesis that the desktop conditions would exhibit higher self-reported motion sickness than the immersive condition. A one-way ANOVA indicated no significant main effect of interface condition on motion sickness, $F(2, 87) = 2.05$, $p = .135$, $\eta^2 = .04$. However, when we collapsed the SDR and LDR conditions into one group and ran a one-tailed, Welch's two samples t-test, there was a significant difference between general desktop motion sickness ($M = 1.50$, $SD = 0.83$) and immersive motion sickness ($M = 1.27$, $SD = 0.45$), $t(87.42) = 1.72$, $p = .044$, $d = .32$. Similar to Study 1, since motion sickness was higher in the desktop condition generally, we also included motion sickness as a covariate in ANCOVA analyses examining spatial learning performance (onsite pointing, wayfinding efficiency) by interface to determine if differences (or lack thereof) in performance was due to motion sickness impacting spatial learning. For onsite pointing, the

ANCOVA revealed that while motion sickness significantly worsened pointing performance, $F(1,87) = 4.39, p = .039$, immersive pointing was still significantly better than desktop pointing ability after including motion sickness as a covariate, $F(1,87) = 19.26, p < .001$. For wayfinding efficiency, we found a significant effect of motion sickness, $F(1,87) = 5.31, p = .024$, but no difference between interfaces after including motion sickness as a covariate ($p = .571$). In sum, while we did not find significant differences in motion sickness across each condition separately, we did not expect an effect of environment size on motion sickness. We did, however, replicate Study 1's findings in that self-reported motion sickness in the desktop conditions was greater than in the immersive condition, and the differences in pointing between interfaces remained after including motion sickness as a covariate.

2.3 Discussion

In Study 2, we accounted for the confounds present in Study 1 by conducting a between-subjects experiment with three conditions in otherwise identical environments: 1 large desktop condition (LDR), 1 small desktop condition (SDR), and 1 small immersive condition (iVR). This design enabled us to examine how different interfaces and environment size, independently, influence spatial knowledge acquisition measured by using pointing accuracy and wayfinding efficiency. We replicated Study One in that onsite pointing ability was significantly better in the immersive condition than both desktop conditions, but wayfinding did not significantly differ among conditions, further supporting the theory that physical locomotion improves survey knowledge acquisition, whereas graph knowledge does not require it for successful wayfinding (Chrastil & Warren, 2013; 2015). However, we found no evidence, at least in this maze environment, that size (10 x 10m vs. 55 x 55m) significantly influences spatial knowledge acquisition via pointing or wayfinding metrics, but

it is to be noted that the larger desktop environments in our studies had a non-significant trend towards worse performance than the small environment conditions. We also replicated the differences in motion sickness between desktop and immersive VR, in that when the LDR and SDR conditions were collapsed together, reported motion sickness was greater in the desktop conditions.

Chapter II General Discussion

Across two studies, we examined spatial knowledge acquisition in identically-structured maze environments and tasks, modifying both the interface (immersive or desktop VR) and environment size (10x10m or 55x55m). In Study 1, we found that performance (measured via onsite pointing and wayfinding) in immersive and desktop environments was significantly correlated (contributing to the general validity of using different interfaces to measure spatial learning). In Study 2 we found that environmental size had no significant impact on any of the spatial learning metrics (in contrast with Proffitt, 2006; Witt, 2011). However, across both studies we found that onsite pointing was significantly better in the immersive conditions than in the desktop conditions, whereas wayfinding did not significantly differ across conditions. Additionally, self-reported motion sickness, albeit higher in the desktop conditions across studies, did not significantly impact performance and results when included as a covariate in analyses.

Limitations

While Study 2 accounted for limitations of Study 1 by using the red brick maze across conditions and including a small desktop version to account for potential influence of environment size, there are still limitations present in this study. The first is that Study 2 did not include a condition in immersive VR in the larger, 55x55m environment. While we could

reliably say that environment size did not seem to matter in the *desktop* conditions, there is evidence to suggest that locomotion may impact ability in larger vs. smaller environments (e.g., Ruddle et al., 2011). Additionally, while the environment size did not matter in this particular maze environment, whereas varying the size of other types of environments (especially those that contain more irregular paths) may have more of an influence on performance.

Future Directions

Despite the clear pattern of our findings across these two studies, there is still a need for future research to paint a more holistic picture of how immersive and desktop interfaces contribute to spatial learning. The first is the inclusion of an immersive condition in a larger, more irregular environment – Ruddle and colleagues found that locomotion in immersive VR improved performance in both smaller and larger gridded environments (2011), but it is unclear if this effect still occurs when participants travel in environments more irregular in structure. Previous research has found that gridded and irregular environments define distinct factors/abilities (Topete et al., 2025; Lader et al., 2025), so it is possible that the effects we found are limited to environments that follow regular, grid-like structures.

Theoretical Implications

This chapter provides direct support for Chrastil & Warren’s previous findings, in that pointing seems to be more reflective as a survey knowledge measure (2013) and wayfinding is more indicative as a measure of graph knowledge acquisition (2015). More specifically, we found that the inclusion of body-based cues significantly improved onsite pointing performance, but had no impact on wayfinding efficiency. Additionally, we found

no evidence, at least in a maze-like environment, that the size of the environment impacts spatial learning performance (in contrast to Proffitt, 2006; Witt, 2011).

Practical Implications

One practical implication of these results is that desktop environments might be sufficient for researchers primarily interested in wayfinding performance, especially in instances where immersive VR is less feasible due to constraints such as space or time. However, immersive VR environments are recommended for acquiring survey knowledge, such as onsite pointing ability, after learning the layout of a novel environment. Finally, immersive ambulatory VR is associated with less motion sickness rates, so can be useful for participant populations that may be more susceptible to motion sickness (e.g., older adults).

Contribution

In summary, this chapter provides clear evidence on the distinction in spatial learning performance in immersive and desktop environments. Specifically, measurements of survey knowledge (e.g., onsite pointing) and motion sickness is better in immersive VR, whereas measurements of graph knowledge (e.g., wayfinding) are not significantly impacted by interface. However, performance is correlated across environments, pointing to the general validity of using either interface to examine spatial learning. This provides positive justification for using desktop environments in Chapter IV (due to restrictions of the study design), but allows us to additionally study changes in survey vs. graph knowledge acquisition across the menstrual cycle in Chapter III.

III. Measuring Navigation Ability and Strategy Across Menstrual Cycle Phases in Young Women.

The purpose of Chapter III is to analyze navigational strategy and performance after learning in immersive virtual environments, across different menstrual cycle phases in young adult women. More specifically, this study measures the associations among 17β estradiol and progesterone and these navigation measures across menstrual cycle phases in matched-complexity immersive VR environments. I will first discuss what we know regarding the rat estrous cycle (the closest analogue to the human menstrual cycle) and its associations with neural and behavioral markers of navigation. Then, I will discuss what is currently known about the human menstrual cycle and general spatial cognition, including small-scale (e.g., mental rotation) and large-scale (navigation) abilities. Finally, I will discuss what gaps in knowledge still exist in regards to human spatial cognition and navigation and the menstrual cycle, and set it as the basis for the current study.

The Rat Estrous Cycle and Navigation Strategy

There is evidence to suggest that the menstrual cycle plays a role in spatial cognition abilities, particularly for navigation strategy. The cleanest evidence is provided by research conducted on rodent models, particularly in female rats. Female rats have an estrous cycle that lasts approximately 4-5 days and is broken up into 4 phases: metestrus/diestrus-1, diestrus/diestrus-2, proestrus, and estrus (Westwood, 2008). During diestrus-1 (day 1), ovarian hormones such as 17β estradiol benzoate (E2) and progesterone (P4) are low. By diestrus-2 (day 2), E2 begins to increase, and by the middle of proestrus (day 3), E2 peaks. By the tail end of the proestrus phase, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin significantly increase, allowing for a quick spike in P4. Between the late proestrus to mid-estrus stage (day 4), ovarian hormones decrease and level

out by the end of estrus and into the next diestrus-1 phase (Andersson et al., 2013, see Chapter I, Figure 1 for a graphical representation).

The hippocampus in particular has been previously demonstrated to be an important brain region for navigation abilities and the formation of accurate mental maps (e.g., O'Keefe & Nadel, 1978; Maguire et al., 2006; Epstein et al., 2017), and is directly impacted by ovarian hormones in female rats. For example, CA1 hippocampal pyramidal cell dendritic spine density fluctuates with the estrous phase - when E2 is high (mid-proestrus), spine density increases. However, when E2 is low or P4 is high for a certain length of time, spine density decreases (Woolley & McEwen, 1993). This finding suggests that E2 directly impacts synaptic plasticity in the hippocampus, which may translate to improvements in hippocampal function in higher E2 phases.

Ovarian hormones in female rats have additionally been associated with behavioral changes in navigation tasks, specifically in navigation strategy. The classic measurement of navigational strategy in rats is through the use of a T- or plus-maze, in which rats are first trained on the location of a food reward that is always located in one adjacent arm of the maze. Then, rats are tested on their strategy use by either being placed in the opposite arm of the maze (for a plus-maze) or by rotating the maze 180 degrees (for a T-maze), and examining what adjacent arm the rat searches for the food (see Chapter I, Figure 2, for a graphical representation of the plus maze). The arm they travel to in the testing phase is designated as either a *response-based strategy* (i.e., they move to the arm that matches with the direction they were originally trained to move, relative to their body/via an egocentric perspective), or a *place-based strategy* (i.e., they move to the arm that matches the initial location of the food reward, relative to extramaze cues/via an allocentric perspective). In

female rats, it has been demonstrated that E2 administration prior to learning in a plus-maze (compared to ovariectomized controls) improved performance when the task required successful place-based strategy use, but hurt performance when the task required successful response-based strategy use (Korol & Kolo, 2002).

Additionally, the dosage and location of E2 administration matters in navigational strategy use. One study found that ovariectomized rats that received higher doses of E2 (90 pg/mL) used more place-based strategies in a plus-maze than rats that received lower doses of E2 (32 pg/mL), who relied more on response-based strategy use (Quinlan et al., 2008). However, it is noted that when dopamine was also introduced to the low E2 group, place-based strategy use increased (whereas its introduction to the high E2 group had no substantial effect), indicating that estradiol may impact navigation strategy use via dopaminergic motivational processes. Finally, in regards to the location of E2 administration, one study found that direct E2 infusions into the dorsal hippocampus of female rats increased place-based strategy use, whereas infusions into the dorsolateral striatum increased response-based strategy use (Zurkovsky et al., 2006). This study demonstrated that the hippocampus is an especially important modulatory neural area for E2 and place-based strategy use, and the dorsolateral striatum is more selective to response-based strategies.

Progesterone (P4), in contrast to E2, seems to have more of an inhibitory effect on place-based strategy use in rat navigation. One study directly tested this effect in ovariectomized rats, finding that while high E2 promotes place-based strategy use in a T-maze environment, the introduction of P4 before testing reversed the effect, and the rats were more likely to use response-based strategies in the maze (Lacasse et al., 2022). Another study found that P4's inhibitory effects on place-based strategy use only existed when E2 was

present, and had no impact on ovariectomized rats without E2 (Gomez-Perales & Brake, 2023). Collectively, this supports the notion that while E2 alone directly influences navigational strategy, it is the dynamic interactions among hormones that shapes navigation strategy (at least, across the estrous cycle in female rats).

In summary, there has been substantial evidence in rodent studies that ovarian hormones play a critical role in shaping navigational processes, particularly in female rats, at both the neural and behavioral levels. Very generally, E2 promotes place-based strategy use in navigation, especially in larger doses and when infused directly into the hippocampus. Dopamine can act to increase place-based strategy use when E2 is low, but otherwise does not impact this strategy when E2 is high. Finally, P4 generally acts as an inhibitory mechanism for place-based strategy use, but only when E2 is also present.

The Human Menstrual Cycle and Spatial Cognition

Findings regarding spatial abilities across the menstrual cycle with women, in contrast to female rats, are not as clear. A major challenge is that lesion studies in humans are primarily unethical (unless it is a medically necessary procedure). The human menstrual cycle has similar patterns to that of the rat estrous cycle, but is significantly longer, lasting on average approximately 28 days, and is broadly categorized into 3 stages: the follicular phase, ovulation, and the luteal phase. The follicular phase begins on the first day of menses (or a period), and lasts until ovulation, for a rough total duration of 14 days. After the menses (which lasts roughly 5-7 days), estradiol and FSH rise, causing the uterine lining to grow and thicken, and follicles in the ovaries develop into an egg. During ovulation (a very short, roughly one day window around day 14), LH has a sharp increase, causing the ovary to release a developed egg. This then leads to a quick, drastic decrease in LH, FSH, and

estradiol. Over the luteal phase (roughly days 15-28), estradiol and progesterone begin to rise in order to prepare the uterine lining for possible pregnancy. If implantation does not occur at the midway point of the luteal phase (midluteal phase), estradiol and progesterone decline once more to prepare for the menses and start the cycle over again (Draper et al., 2018, see Chapter I, Figure 3, for a graphical representation).

Research that has previously examined the menstrual cycle and spatial cognition ability has been primarily dedicated to measuring aspects of small-scale spatial ability, such as mental rotation or other pen-and-paper tasks. For example, a preliminary study found that spatial performance – as measured by hidden figures, rod-and-frame, and spatial relations tests – was better in women when they were in their early follicular (menses) phase, than when they were in their midluteal phase (Hampson, 1990). In this same study, the opposite pattern was found for measures related to verbal-articulation, fine motor skills, verbal fluency, and perceptual speed (performance was better in the midluteal phase). From these findings, it was suggested that gonadal hormones (both estradiol and progesterone) enhance abilities that typically favor females (such as articulation, fluency, and perceptual speed), and impair abilities that favor males (such as spatial abilities and abstract reasoning).

Follow-up research examining the menstrual cycle and small-scale measures of spatial ability found similar patterns, especially in regards to mental rotation ability. While one study did not replicate Hampson's (1990) finding with the Hidden Figures test (performance did not significantly differ by menstrual cycle), they did find that mental rotation performance was significantly better in the menses, rather than midluteal, phases of the menstrual cycle in young women (Hausmann et al., 2000). Multiple studies examining the menstrual cycle and mental rotation have largely replicated these results (Moody, 1997;

McCormick & Teillon, 2001; Maki et al., 2002; Peragine et al., 2020; Hromatko & Tadinac, 2024 [for 3D mental rotation]). One study examined estradiol concentrations directly, rather than by classifying cycle phase, and found similar results, in that high estradiol phases resulted in worse mental rotation performance than low estradiol phases (Hampson et al., 2014). Some studies did not replicate these results (Schöning et al., 2007; Kozaki & Yasukouchi, 2009; Hromatko & Tadinac, 2024; Pletzer et al., 2024), but it is to be noted that one study found that the menses performance advantage was exclusive to 3D, but not 2D, mental rotation ability (Hromatko & Tadinac, 2024). Finally, one study found an inverse U-shape relationship between estradiol and mental rotation, where performance was better in low estradiol phases, decreased in moderate phases, and then improved again in high estradiol phases (Courvoisier et al., 2013; similar to the pattern of findings with McCormick & Teillon, 2001). In sum, while there are some mixed results in the relationship between the menstrual cycle and mental rotation performance, it is more commonly found that low estradiol phases perform better than higher estradiol phases (or at least, in phases where both estradiol and progesterone are elevated). It is to be noted that this general finding is in direct contrast with rodent studies, in which spatial performance (measured via navigation strategy) is better when estradiol is high.

Finally, there is a body of work that has examined the relationship between menstrual cycle and sex differences in mental rotation. Notably, some studies found that there was only a significant male advantage in performance when compared to women in their midluteal phases, but that male advantage was no longer significant when compared to women who were tested during their menses (Moody, 1997; McCormick & Teillon, 2001; Schöning et al., 2007; Peragine et al., 2020). However, a couple other studies found that men performed

significantly better than women regardless of their menstrual cycle phase (Kozaki & Yasukouchi, 2009; Courvoisier et al., 2013), so the exact nature of this sex difference is not cleanly established.

While there has been a significant body of work that has examined small-scale spatial ability and variations in performance via the menstrual cycle, there has been far less research examining these associations with large-scale spatial ability (i.e., navigation). Brown et al (2023) found that path integration – the ability to continuously update one’s position and orientation in space only from self-motion, especially proprioceptive and vestibular cues (Mittelstaedt & Mittelstaedt, 1982; Loomis et al., 1993) – differed by cycle phase, in that women in their ovulatory window had worse performance than women in their early follicular and midluteal phases. However, women in their ovulatory window performed better than in other cycle phases in this task when a landmark was present, suggesting that spatial ability is differentially associated with the menstrual cycle in women. The researchers found no other significant differences in performance by menstrual cycle in other spatial tasks (cognitive map formation, and the four mountains test).

Aside from the previous study which utilized path integration, studies of spatial navigation performance across the menstrual cycle – while limited – have been primarily concerned with navigational strategy, specifically place-based versus route/response strategies. For example, one study found that women in their midluteal (high estradiol and progesterone) phase used more place-based strategies in a desktop, 8-arm radial maze than women in their early follicular or ovulatory phases, who used more response-based strategies (Hussain et al., 2016). Another study used a virtual Morris Water Maze task and found a somewhat conflicting pattern, in that women classified into a higher-estradiol group alone

used more place-based strategies than women classified into a lower-estradiol group (Patel et al., 2022). Other studies examined women in their early follicular and midluteal phases, measuring 2D navigation based on a combination of an 1) allocentric (cardinal directions) or egocentric (left, right, straight) perspective and 2) Euclidean (relative to distance, place-based) or landmark (relative to landmarks, response-based) strategy directions. One study found that women in their midluteal phase had better performance using the landmark strategy than when they were in their early follicular phase (Scheuringer & Pletzer, 2017). A follow-up study that used the same 2D task as Scheuringer and Pletzer (2017), but only using the egocentric perspective, found that women in the ovulatory window had better performance than women in their early follicular or midluteal phases when directions contained Euclidean strategy information, but did not find any other significant differences in menstrual cycle phase (Bernal et al., 2020). Another study found that the ovulatory window was associated with elevated hippocampal activation during the same navigation task, whereas the midluteal phase was associated with decreased activation in the left hippocampus, but did not find any significant differences in behavioral performance (Pletzer et al., 2019). While this finding is in line with rodent research seeing increased hippocampal spine density in higher estradiol concentrations (Woolley & McEwen, 1993), these studies collectively paint a complicated, unclear picture of how the menstrual cycle is associated with spatial navigation ability and strategy.

Aside from the sparse literature examining spatial navigation and the menstrual cycle, there are also limitations of the methodologies used. For example, all previous studies directly examining menstrual cycle phases used desktop, online environments to measure navigational strategy (Hussain et al., 2016; Scheuringer & Pletzer, 2017; Pletzer et al., 2019;

Bernal et al., 2020; Patel et al., 2022; Brown et al., 2023). Given that desktop environments do not allow for full field of view in navigation or the availability of body-based senses from physical locomotion, it is unknown whether the menstrual cycle impacts spatial learning tasks more impacted by body-based cues, such as the ability to point to objects after learning an environment (see Chapter II Results; Chrastil & Warren, 2013).

Additionally, previous studies examining large-scale spatial ability differ in how they measure cycle phases. For example, one study only used a self-report measure of cycle phase history (Brown et al., 2023), limiting the conclusion that the proper cycle phase windows were actually captured (as the study was administered completely online). Another study used both self-report and hormonal assessments of ovarian hormones (via saliva assays), but only examined the early follicular and midluteal phases (Scheuringer & Pletzer, 2017), which confound differences in estradiol and progesterone in that the midluteal phase is characterized by higher concentrations of both estradiol and progesterone, rather than estradiol alone. Finally, some studies that used both self-report and hormonal assessments of cycle phase, and included the ovulatory window are additionally confounded in that they used a between-subjects (cross-sectional) design, so women were not included at multiple time points in their cycle (Hussain et al., 2016; Bernal et al., 2020; Patel et al., 2022), confounding state and trait effects of estradiol. Only one study to date included all these components (self-report and hormonal confirmation of cycle phase, the inclusion of the ovulatory window, and tested women at multiple phases of their cycle), but is still limited due to only measuring one desktop spatial task (Pletzer et al., 2019).

Current Study

The current study addresses the gaps from previous research examining navigation and spatial learning at different phases of the human menstrual cycle. Specifically, this study examines navigation ability and strategy after learning in an immersive VR environment, for women in both the high and low estradiol phases of their menstrual cycle (ovulatory window and early follicular phase respectively), when progesterone should not significantly differ. To confirm cycle phase windows, we used self-report measures of cycle history (at least 3 months of cycle tracking), saliva assessments of 17β estradiol and progesterone, and daily LH testing (to confirm the ovulatory window).

While measuring navigation ability and strategy was the primary focus of this study, we additionally included a mental rotation task as a small-scale measure of spatial ability, which, in contrast with navigation performance is typically found to be better at menses (i.e. when estradiol is low), and other general cognitive tasks (processing speed, executive function, episodic memory, inhibition, working memory) to delineate if spatial abilities are selectively modulated by the menstrual cycle, or if cognition is globally impacted, as prior research has conflicting results in this regard (Hampson, 1990; Sawicka et al., 2025; see Jang et al., 2025 for a meta-analysis). Finally, we administered a number of self-report measures, including sense of direction, spatial anxiety, exploration tendency, navigational growth mindset, GPS dependency and use, mindfulness, a measure of gender stigma threat in women, and reproductive health history.²

It was hypothesized the early follicular phase/menses would result in more route-based strategy use (indicated by relying on tracing previously learned routes) and worse spatial knowledge acquisition after learning an immersive VR environment (measured by

² These were part of a separate study and will be reported elsewhere.

wayfinding excess distance and onsite pointing ability) than higher menstrual cycle phases, consistent with rat studies (e.g., Korol & Kolo, 2002; Bernal et al., 2020). However, we anticipated the opposite pattern of results with mental rotation performance, in that we expected to replicate previous work finding that mental rotation ability performance would be significantly better in the early follicular phase, when estradiol is low (e.g., Moody, 1997; Hausmann et al., 2000; Maki et al., 2002; Hampson et al., 2014; Peragine et al., 2020).

Method

Participants

Participants were adult, pre-menopausal women in the Santa Barbara area. Participants were screened (via a Qualtrics survey) prior to participation and were required to be naturally cycling (i.e., not on any form of hormonal contraceptive method), regularly cycling (cycle lengths averaged between approximately 21-35 days and did not vary in length by more than 7 days, established by at least 3 previous menstrual cycle start dates), a minimum of 11 cycles in the last 12 months, did not have a reported endocrine disorder (e.g., PCOS, endometriosis, fibroids, ovarian cysts), and reported no current steroid medication use (such as hydrocortisone). By the time recruitment concluded for this report, 216 people had completed the screening survey in its entirety, with 67 participants considered eligible to participate for the study. Of those 67 eligible participants, 33 were confirmed and recruited to participate in the study.

Of the original 33 participants that were screened and recruited to participate, 1 was excluded from analyses due to reporting the use of an emergency contraceptive a couple days prior to her ovulatory window session. One additional participant was excluded due to not returning for the second session, leading to a final sample size of 31 participants analyzed

(ages 19-37 years, $M = 23.48$, $SD = 4.83$). Participants were counterbalanced for the order in which they came in at each cycle phase (early follicular or ovulatory window), and the version of the immersive DSP that was completed first (red brick or grey wall) as closely as possible, with 13 participants who started in their early follicular phase (6 with the red brick DSP first), and 18 participants who started in their ovulatory window (10 with the red brick DSP first).

Materials

Participants were administered the following tasks. Similar to Chapter II, participants were also administered the SBSOD (Hegarty et al., 2002), GPS Usage (Topete et al., 2024), GPS Dependency, Spatial Anxiety, Growth Mindset in Navigation, and Exploration Tendency scales (He & Hegarty, 2020). Additionally, a measure of mindfulness via the Mindful Attention and Awareness Scale (MAAS, Brown & Ryan, 2003) and a measure of gender stigma via the Stigma-Consciousness Questionnaire for Women (SCQ-W, Brown & Pinel, 2003) were administered as part of a separate study, and will be reported elsewhere.

Measure of Navigation Ability & Strategy. The Dual Solution Paradigm (DSP; Marchette, Bakker, & Shelton, 2011; Boone et al., 2018) was administered to assess navigation strategy after learning a novel environment. The DSP environments followed the same format for environment layout and structure as Chapter II (for both the red brick and grey wall versions), with the primary difference being that the environments were only administered in ambulatory immersive VR (so the alternate version was consequently scaled down to a 10 x 10m space). In the immersive DSP, participants were fitted with a head mounted display (HMD) and learned the environments by walking through and viewing the environment, and used a controller to point and click to various objects in the environment.

The learning and testing procedures followed an identical format as the ambulatory immersive maze, outlined in Chapter II, Study 1.

Mental Rotation. An online modified, 10-item version of the Vandenberg and Kuse (1978) mental rotations test (Munns & Hegarty, 2026) was included to measure mental rotation ability. In this task, participants are given a reference image of a three-dimensional object (of the type used by Shepard & Metzler, 1971) and asked to identify, out of four possible images, which two show the same object, but rotated at a different angle. There are always two correct answers and two distractor items. The distractor items are always mirror-distractors of the reference image (whereas the original test has ten additional items that contain structural distractors). Performance in each item is either scored as a 1 (both correct answers, and only those answers, were selected) or a 0 (for any responses where they did not get exactly both correct answers), and then summed. Total scores range from 0 to 10, where higher scores indicate better performance.

NIH Cognitive Toolbox Battery. Measures of general cognitive abilities were also included from the NIH Cognitive Toolbox Battery. These tasks included the Dimensional Change Card Sort Test (executive function), Face Name Associative Memory Exam Test (FNAME, episodic memory), Flanker Inhibitory Control and Attention Test (inhibition), List Sorting Working Memory Test (working memory), Oral Symbol Digit Test (processing speed), Picture Sequence Memory Test (episodic memory), and the Rey Auditory Verbal Learning test (RAVL, immediate memory). This toolbox has been validated for its test-retest reliability, as well as convergent and discriminant construct validity (Weintraub et al., 2013).

Measure of Reproductive History. A series of questions was administered to examine a woman's reproductive history. These items included previous history of endocrine disorders

(endometriosis, fibroids, ovarian cysts, PCOS, pelvic inflammatory disease), as well as information about their menstrual cycles (age of first period, last 3 period start dates if known, menstrual cycle regularity), if they are currently pregnant, hormonal contraceptive use (including emergency contraceptive use), questions related to menopausal symptoms, and use of hormone replacement.

Hormone Analysis. Saliva samples were collected in the same fashion as Chapter II, that is, both before (T1) and after (T2) completing the tasks with each environment and were stored in a -80 freezer in the Biobehavioral Health Laboratory at UC Santa Barbara. In this study, samples were collected to primarily assay ovarian hormones, specifically 17β estradiol and progesterone concentrations in women at each menstrual cycle phase.

Prior to assay, samples were thawed and centrifuged at 3500 rpm for 10 minutes to separate the pure saliva from mucus and other suspended particulates. Assays were processed in duplicates using competitive enzyme immunoassay kits (1-3702 for estradiol, 1-1502 for progesterone, Salimetrics LLC, State College, PA). Using these kits, we could reliably measure salivary 17β -estradiol concentrations up to 32 pg/mL (with a minimum sensitivity of 0.1 pg/mL), and salivary progesterone concentrations up to 2430 pg/mL (with a minimum sensitivity of 5 pg/mL). For this study, estradiol had an intra-assay coefficient of variation (CV) of 2.23% and inter-assay CV of 3.85%; progesterone had an intra-assay CV of 6.67% and inter-assay CV of 3.65%.

Procedure

The IRB reviewed and approved this study prior to the recruitment and collection of human subjects. Prior to any in-person data collection, interested participants were first given a screening survey via Qualtrics to determine eligibility, where they viewed and signed the

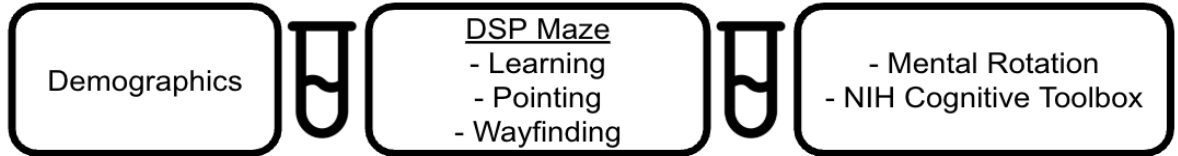
informed consent for the whole study. Next, participants responded to the self-report spatial (GPS dependency, GPS usage, spatial anxiety, SBSOD, and exploration tendency) and MAAS questionnaires in a randomized order. Demographics were presented next (ADHD diagnosis, any current steroid, stimulant, or non-stimulant use, previous exposure to immersive VR, major, age, sex, gender, race, ethnicity, primary language spoken at home, and present religion), followed by the gender stigma and reproductive history questionnaires. Once all questionnaires were completed, participants input their email for follow-up, and were contacted if they qualified for the study.

Participants who qualified then scheduled their first session with an experimenter, counterbalanced for menstrual cycle phase order (early follicular vs. ovulatory window). For those scheduling their first session within their ovulatory window, participants came to the lab prior to the end of their previous period and were provided with 2 weeks' worth of LH tests. Participants provided with LH tests were instructed to take the tests daily at home in the afternoon, until it was confirmed that an LH spike occurred. Ovulatory window sessions were scheduled approximately one day prior to the participant's estimated LH spike, as estradiol has been previously noted to increase prior to LH (Draper et al., 2018). Participants were required to notify an experimenter: 1) when the spike occurred, and 2) if LH started rising more than 1 day prior to their scheduled ovulatory window session. Participants within their early follicular phase were scheduled within days 2-5 of their period.

For the first session, participants came to the virtual environment room, one at a time, within their early follicular or ovulatory cycle phase. Sessions were time-locked for each participant to the afternoon, at least a few hours after waking time. After providing follow-up consent to the study, participants provided the T1 saliva sample. As in Chapter II,

participants collected the sample for 2 minutes, and an experimenter noted the end time of sample collection in a participant log (see Figure 9 for a graphical representation of the procedure).

Figure 9. General Procedure Outline for Each Study Session.



Participants were then administered the DSP task with one of the immersive environments (either the red brick or grey wall), and completed the learning, pointing and wayfinding tasks in that order. After the DSP tasks concluded, participants provided the second saliva sample (T2). Following this, participants completed the mental rotation task on a computer. First, participants completed 2 practice items after reading instructions to confirm they understood the task, and were provided feedback on these items. Then, the 10 test items were presented in a randomized order, in which participants had up to one minute to respond to each question before the next item loaded. After completing the 10 items, participants were provided their final score on the task as feedback.

Next, participants completed the NIH Cognitive Toolbox Battery on a laboratory-provided iPad. More specifically, they completed the tasks in a set order: Dimensional Change Card Sort, FNAME first exposure, Flanker test, List Sorting Working Memory, Oral Symbol Digit, FNAME delayed test, Picture Sequence Memory, and RAVL. Feedback was only given to participants for practice items (dimensional card sort, flanker, list sorting working memory, oral symbol digit, and picture sequence memory).

Upon completion of these tasks, participants scheduled their second session date, during either their follicular or luteal phase (whichever phase had not been tested in the first session). If they were in their follicular phase for their first session, participants were also provided with the 2 weeks' worth of LH tests, to begin taking daily once their menstrual cycle concluded (an identical procedure to that described above). Participants were scheduled in their ovulatory window approximately 1 day prior to the estimated LH spike, and continued to take LH tests after their session to confirm the spike occurred after the session. For those who completed the first session in their ovulatory window, they were scheduled to participate in their second session within days 2-5 of their anticipated upcoming period.

For the second session, participants came in to the virtual environment room at a similar time window as their first session (i.e., in the early to late afternoon) and were administered a similar protocol as the first session, except that the second immersive maze environment was used (original red brick or alternate grey wall, whichever environment was not used in the first session), participants are in a different menstrual cycle phase than the first session. Most of the remaining tasks contained the same items, with the exception of the picture sequence memory task (in which the items were of different scenarios).

Upon completion of this second session, participants were thanked for their time and provided full payment for both sessions.

Analysis Plan

The exclusion criteria for participants excluded were those who: 1) did not complete both study sessions in their entirety, 2) reported taking any form of hormonal contraceptive, including emergency contraceptives, 3) had an average cycle length that exceeded approximately 35 days, or had more than 7 days of variability between cycles, 4) had a

history of any endocrine disorder (e.g., PCOS, endometriosis, ovarian cysts, fibroids), 5) reported to having had less than 11 menstrual cycles in a 12-month timeframe, 6) reported current use of steroid medication use, and 7) have been identified as not being within their respective cycle-phase stage (early follicular or ovulatory). For hormone assessments, samples were excluded from analyses if they: 1) provided a contaminated saliva sample (e.g., plasma or excessive particulates were detected); 2) had estradiol or progesterone concentrations that had a CV that exceeded 15 for estradiol, or 20 for progesterone.

All measures were scored in the same fashion as Chapter II, which includes onsite pointing, wayfinding excess distance, and the self-report questionnaires. Navigation strategy (solution index/SI) was calculated to examine place-based/shortcutting behavior in wayfinding. SI is a classifier system, calculated as the number of shortcuts taken over the total number of successful wayfinding trials per participant. SI values range between 0 to 1, where 0 indicates no shortcut use across successful trials, and 1 indicates that the participant took the shortcut on every successful wayfinding trial. Each trial was first classified via a Fréchet distance metric, which compares the trajectory of a participant's trial to a predefined trajectory (such as the previously learned route and the shortest possible route), and then calculates a similarity value for each predefined trajectory. The trial was then assigned as a "shortcut," "learned route," or "reverse-learned route" based on whatever Fréchet distance value was lowest (or least deviation from the predefined trajectory) in the given trial.

General cognitive tasks administered via the NIH Cognitive Toolbox battery were scored based on the "Age Adjusted Standard Score" value, where performance (when adjusted for age) is scored based on the average national performance (centered around a value of 100). Higher scores indicate better performance.

For hormone assessments, salivary estradiol and progesterone concentrations were excluded (or re-assayed) if they exceeded a CV value of 15 for estradiol, and 20 for progesterone. State-based hormone concentrations were measured as the average concentrations of estradiol and progesterone across both cycle sessions. Trait-based measures were either run as their raw concentrations (in pg/mL) for general t-tests, or for linear mixed effects models (LMMs), as the raw concentration in a particular session subtracted from the state-based, average concentration for each participant (within-subject centered).

Analyses include paired samples t-tests, which were conducted to determine if ovarian hormone concentrations (estradiol, progesterone) differed between cycle phase as a manipulation check for the study. Additionally, paired samples t-tests were conducted where the independent variable was cycle-phase (follicular and luteal), and the dependent variables included wayfinding SI (to assess place vs. response-based strategy use), wayfinding excess distance, and onsite pointing ability.

Additionally, linear mixed effect models (LMMs) were conducted to measure state- and trait-based ovarian hormone concentrations (estradiol, progesterone) and their associations with wayfinding excess distance, SI, and onsite pointing ability. Random effects structures for mixed-effects models were defined following the guidelines set by Bates et al. (2015), employing the maximal random effect structure that had no convergence issues. The models were run in R using the *lme4* package in R (Bates et al., 2015). Finally, paired samples t-tests were additionally used to measure differences in performance in other cognitive measures (e.g., mental rotation, processing speed, inhibition, working memory, episodic memory, etc.) across cycle phases.

Results

Manipulation Check - Estradiol and Progesterone by Cycle Phase

First, we sought to validate that the different menstrual cycle phases (early follicular, ovulatory window) were properly captured by measuring estradiol concentrations in each phase, and hypothesized that estradiol concentrations would be higher in the ovulatory window than the early follicular phase. Descriptive statistics for estradiol concentrations in each cycle phase window are provided in Table 3. To test this hypothesis, we conducted a one-tailed paired samples t-test with estradiol concentrations in each estimated cycle phase. Estradiol concentrations in the ovulatory window were significantly higher than in the early follicular phase, $t(30) = -2.66, p = .006, d = -0.38$, see Figure 10A. In summary, our hypothesis that salivary estradiol would be higher in the ovulatory window was supported³.

Table 3. Descriptive Statistics for Estradiol (N = 31) and Progesterone (N = 24) Concentrations by Reported Cycle Phase.

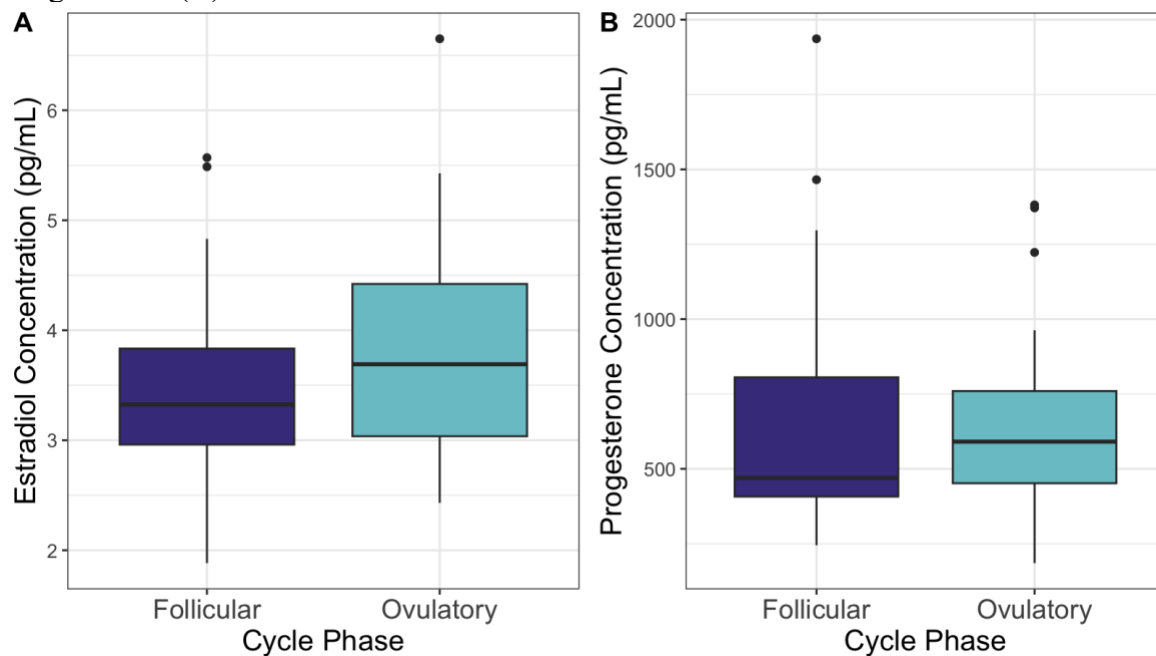
<i>Cycle Phase</i>	<i>Estradiol (pg/ml)</i>		<i>Progesterone (pg/ml)</i>	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Early Follicular	3.46	0.83	651.26	429.18
Ovulatory Window	3.82	0.99	641.59	315.57

Progesterone concentrations were also examined by cycle phase to determine if there were significant differences between cycle phases. We expected no significant differences in progesterone concentrations between cycle phases, as we measured cycle phase windows that

³ It is to be noted that while the hypothesis was supported, our average estradiol concentrations deviated from Salimetrics' example estradiol concentration ranges, especially in the case of the follicular phase. The Salimetrics example range for the follicular phase was $M = 1.35$ pg/mL, $SD = 0.80$ pg/mL, and the mid-cycle was $M = 2.97$ pg/mL, $SD = 1.58$ pg/mL. While our concentrations were higher and less variable between cycle phases, it is possible that our sample may not be fully representative of the exact cycle phases we aimed to measure (e.g., women at the end of their menses may have had rising estradiol, and women in the ovulatory window may not have been in the peak estradiol window).

should vary only in estradiol concentrations. Descriptive statistics of progesterone concentrations can be found in Table 3. A paired samples t-test with progesterone concentrations in each estimated cycle phase found that progesterone did not significantly differ between cycle phases, $t(24) = 0.14$, $p = .889$, $d = 0.02$, see Figure 10B. Appendix B contains individual line plots in progesterone concentrations in their early follicular and ovulatory window phases.

Figure 10. Ovarian Hormone Concentrations by Cycle Phase (pg/mL) for Estradiol (A) and Progesterone (B).



Navigation and Cycle Phase

It was hypothesized that women in the ovulatory window, would demonstrate better pointing ability, be generally more efficient in wayfinding, and take more shortcuts in the DSP environments than when they were in the early follicular phase/menses, due to having higher estradiol concentrations in the ovulatory window. Descriptive statistics for wayfinding

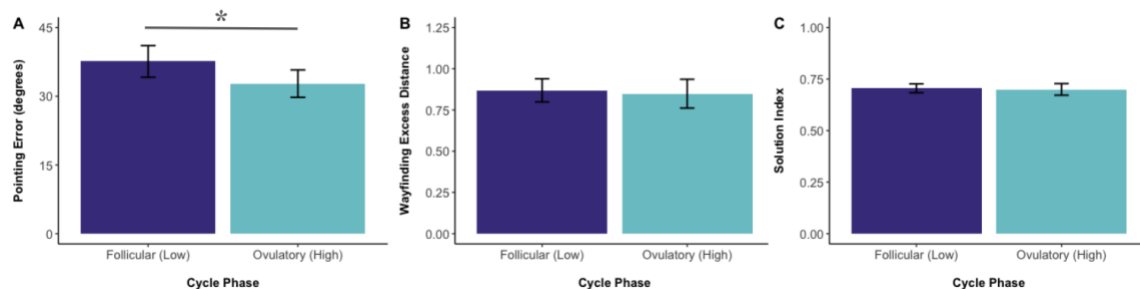
onsite pointing error, excess distance, and solution index/shortcutting use are provided in Table 4.

Table 4. Descriptive Statistics for Navigation Performance by Cycle Phase.

<i>Variable</i>	<u><i>Early Follicular</i></u>		<u><i>Ovulatory Window</i></u>	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Onsite Pointing	37.61	19.24	32.76	16.68
Wayfinding Excess Distance	0.87	0.39	0.85	0.49
Solution Index	0.71	0.12	0.70	0.16

One-tailed paired samples t-tests revealed that onsite pointing angular error was significantly lower in the ovulatory window than in the early follicular phase, $t(30) = 1.86$, $p = .037$, $d = 0.26$ (see Figure 11A). However, wayfinding excess distance did not significantly differ in performance between cycle phases, $t(30) = 0.22$, $p = .413$, $d = 0.04$ (see Figure 11B), and neither did solution index/shortcutting use, $t(30) = 0.15$, $p = .560$, $d = 0.04$ (see Figure 11C). In summary, our hypothesis was partially supported – while onsite pointing performance was significantly better in the ovulatory window (supporting the hypothesis), wayfinding performance (excess distance and solution index) did not significantly differ between cycle phases.

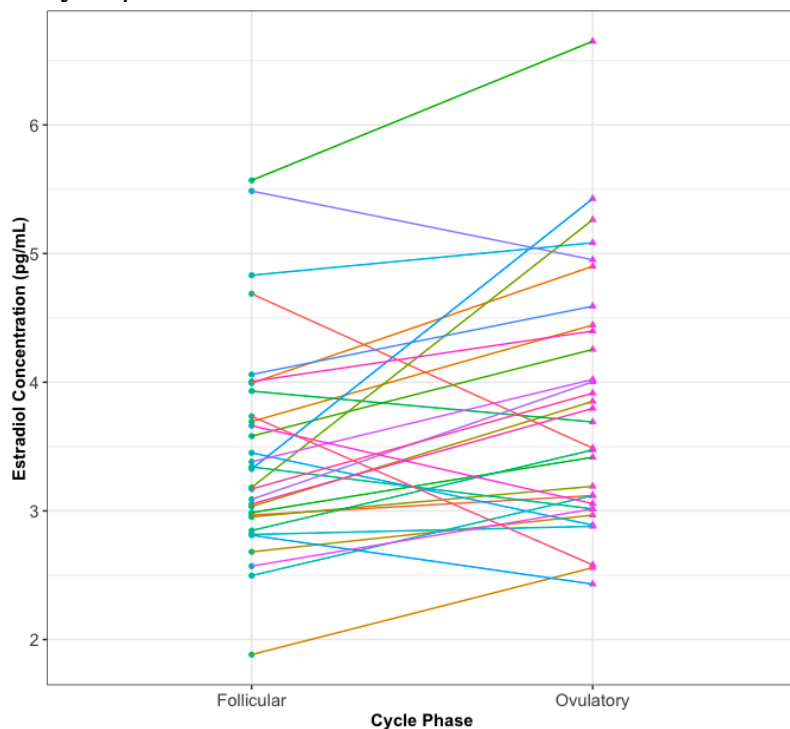
Figure 11. Bar Plots for Average Onsite Pointing Error (A), Wayfinding Excess Distance (B), and Solution Index (C), with Standard Errors.



Note: * $p < .05$.

We did note that a subset of participants actually had *decreased* estradiol concentrations between the early follicular and ovulatory window, meaning we likely did not properly capture one or both cycle phase windows in those participants (see Figure 12). However, even when removing them from analyses (and only considering those who had higher estradiol in the ovulatory window), we find the same pattern of results as when all participants were included. Additionally, these results did not change even when controlling for order effects and which version of the maze they completed first (red brick or grey wall).

Figure 12. Individual line plots for estradiol concentrations in the early follicular and ovulatory window cycle phases.

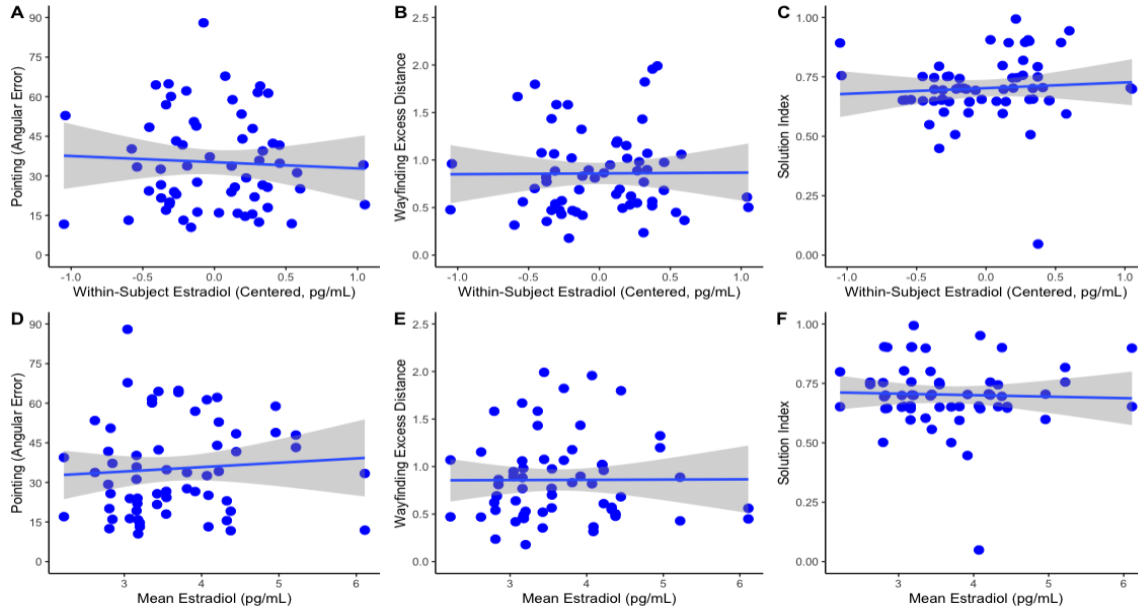


Navigation and Ovarian Hormones

In addition to analyses by cycle phase, we also examined continuous ovarian hormone concentrations (state- and trait-based levels of estradiol and progesterone) and their general relationships to onsite pointing ability, wayfinding excess distance, and

SI/shortcutting use. This was tested via linear mixed effect regression models (LMMs), to account for the multilevel structure of the data. We conducted models predicting each target outcome measure (onsite pointing error, excess distance, and SI) from within-subject centered estradiol (session-level estradiol measure) and subjects' average estradiol concentration (subject-level estradiol measure). We hypothesized that estradiol would generally be positively associated with each navigation outcome measure, both at the session- (state) and subject- (trait) levels. However, results indicated that pointing error was not significantly predicted by within-subject estradiol, $\beta = -.05, p = .484$ (see Figure 13A), nor average estradiol, $\beta = .08, p = .655$ (see Figure 13D). Wayfinding excess distance was also not significantly predicted by within-subject estradiol, $\beta = .01, p = .941$ (see Figure 13B), nor average estradiol, $\beta = .005, p = .974$ (see Figure 13E). As with the other two measures, SI also was not significantly predicted by within-subject estradiol, $\beta = .07, p = .581$ (see Figure 13C), nor average estradiol, $\beta = -.04, p = .778$ (see Figure 13F). In sum, our hypothesis was not supported, as continuous estradiol concentrations (state and trait) were not significantly associated with any spatial navigation outcome measure.

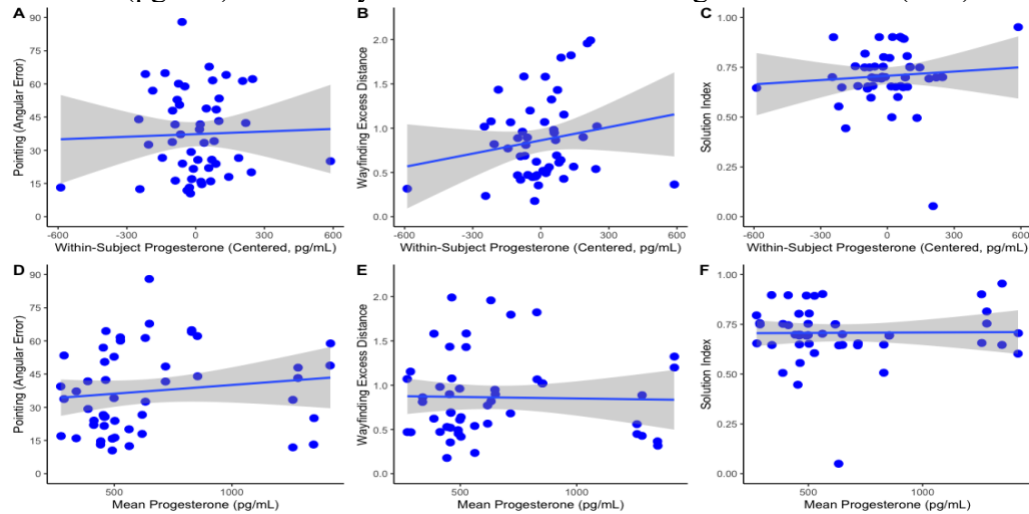
Figure 13. Regression Plots Examining Within-Subject Estradiol Concentrations (pg/mL) by Cycle Phase for Each Navigation Measure (A-C), and Mean Estradiol Concentrations (pg/mL) Across Both Cycle Phases for Each Navigation Measure (D-F).



While we had no specific expectations with regard to progesterone (as we found no difference in concentrations between cycle phases), we examined if state and trait progesterone concentrations were generally related to spatial knowledge acquisition after learning an environment. To do this we ran the same series of LMMs as with estradiol, predicting each target outcome measure (onsite pointing error, excess distance, and SI) with within-subject centered progesterone (session-level progesterone measure) and subjects' average progesterone concentration (subject-level progesterone measure). Onsite pointing was not significantly predicted by within-subject progesterone, $\beta = .03, p = .691$ (see Figure 14A), nor average progesterone, $\beta = .14, p = .466$ (see Figure 14D). Similarly, wayfinding excess distance was not significantly predicted by within-subject progesterone, $\beta = .18, p = .116$ (see Figure 14B), nor average progesterone, $\beta = -.03, p = .883$ (see Figure 14E). Finally, SI was not significantly predicted by within-subject progesterone, $\beta = .08, p = .580$ (see Figure 14C), nor average progesterone, $\beta = .01, p = .944$ (see Figure 14F). In sum, we found

no relationship between progesterone (state and trait) with any of the spatial navigation outcome measures.

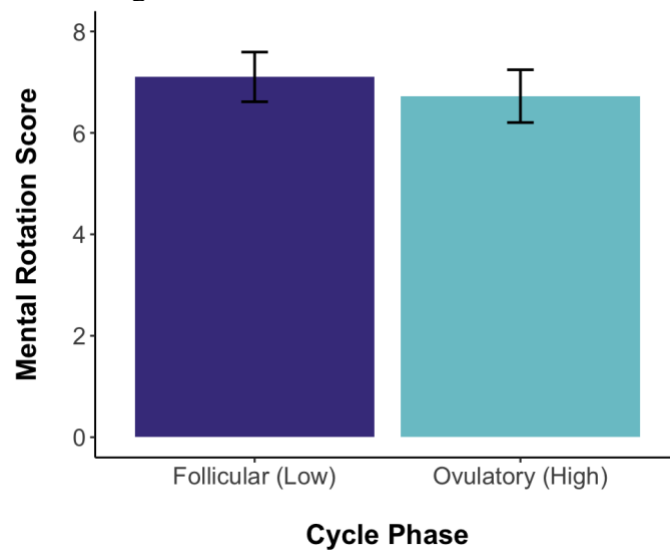
Figure 14. Regression Plots Examining Within-Subject Progesterone Concentrations (pg/mL) by Cycle Phase for Each Navigation Measure (A-C), and Mean Progesterone Concentrations (pg/mL) Across Cycle Phases for Each Navigation Measure (D-F).



Mental Rotation, General Cognitive Measures and Cycle Phase

In regards to mental rotation, we anticipated to replicate previous research (e.g., Moody, 1997; Maki et al., 2002; Hampson et al., 2014; Peragine et al., 2020) in that mental rotation abilities would be higher in the early follicular phases than in the ovulatory window. A one-tailed, paired samples t-test revealed that mental rotation abilities did not significantly differ between cycle phases, and had a small effect size (see Table 5 for descriptive and inferential statistics, and Figure 15 for a graphical representation of performance in each phase). In sum, our hypothesis was not supported by the current data, though trends were in the predicted direction (better performance at the early follicular stage when estradiol is low, in contrast with pointing performance which was better at the ovulatory phase when estradiol is high).

Figure 15. Bar Plot for Average Mental Rotation Performance, with Standard Errors.



We also examined whether other aspects of cognition, measured by the NIH Cognitive Toolbox varied by cycle phase, including executive function (Dimensional Card Change Sort), inhibition (Flanker), working memory (List Sorting Working Memory), processing speed (Oral Symbol Digit), verbal learning (Rey Auditory Verbal Learning), and 2 measures of episodic memory (the FNAME and Picture Sequence Memory tests). Two-tailed, paired samples t-tests revealed no significant differences in performance between cycle phases in any of the measures, and had small effect sizes (see Table 5 for descriptive and inferential statistics). In summary, we found that other general aspects of cognition were not significantly influenced by cycle phase.

Table 5. Descriptive Statistics, Paired Samples t-tests, and Effect Sizes for General Cognition Measures Between Cycle Phases.

<i>Variable</i>	<i>Early Follicular</i>	<i>Ovulatory Window</i>	<i>t</i>	<i>df</i>	<i>p</i>	<i>d</i>
	<i>M (SD)</i>	<i>M (SD)</i>				
Mental Rotation	7.10 (2.64)	6.72 (2.80)	0.93	28	.180	0.17
DCCS	105 (12.43)	107.58 (18.33)	-1.09	30	.284	-0.20
Flanker	107.65 (14.67)	109.52 (14.57)	-1.08	30	.291	-0.19
LSWM	107.16 (13.28)	110.06 (11.50)	-1.44	30	.160	-0.26
OSD	115.20 (14.95)	113.57 (14.86)	0.82	29	.417	0.15
RAVL	120.47 (19.63)	118.40 (21.62)	0.52	29	.608	0.09
FNAME	113.64 (11.94)	113.04 (14.01)	0.19	27	.851	0.04
PSM	111.93 (15.08)	107.10 (13.41)	1.71	28	.098	0.32

Note: DCCS = Dimensional Card Change Sort, LSWM = List Sorting Working Memory, OSD = Oral Symbol Digit, RAVL = Rey Auditory Verbal Learning, FNAME = Face Name Associative Memory Exam, PSM = Picture Sequence Memory.

Discussion

This study examined whether spatial navigation strategy and ability vary across different phases of the menstrual cycle after learning in novel, immersive VR environments. Specifically, we measured healthy young women at two phases of the menstrual cycle that are characterized by either high (ovulatory window) or low (early follicular/menses) estradiol concentrations, and validated self-report measures of cycle phase with salivary estradiol and progesterone measurements. We additionally included a measure of small-scale spatial cognition (mental rotation), as well as several other measures of general cognition.

First, we were able to successfully target women in their high and low estradiol cycle phase windows, through confirmation of both self-report cycle history and saliva assessments, revealing that estradiol was higher in the ovulatory window but progesterone concentrations did not differ between phases. In regards to spatial navigation ability and

strategy, we found an interesting distinction in which aspects of spatial learning vary across different menstrual cycle phases. First, we found that after learning in an immersive VR maze, women performed better in an onsite pointing task when in their ovulatory window than the early follicular phase. However, neither measurement of wayfinding (efficiency or place-based/shortcutting strategy use) significantly differed between cycle phases. Given that pointing is proposed to be a metric of survey knowledge (see Chapter II; Chrastil & Warren, 2013) and wayfinding is proposed to be a metric of graph knowledge (see Chapter II; Chrastil & Warren, 2015), we find some preliminary evidence that the ovulatory window – at least in human women – may improve fine-tuned metrics of survey knowledge acquisition, but have no impact on wayfinding or strategy preference relative to the early follicular phase. Essentially, this suggests the knowledge required to successfully navigate on a daily basis (graph knowledge) is not impacted by short-term changes in estradiol in young women, but the *quality* of the metric cognitive map is improved when women are in phases characterized by high estradiol and low progesterone, relative to low concentrations of both.

Additionally, we found that continuous estradiol and progesterone concentrations did not predict any of our spatial learning outcome measures (onsite pointing, wayfinding efficiency, and place-based strategy use) at either the state or trait levels. This is surprising, especially given that we found estradiol was higher in the ovulatory window, and other studies found that in general higher estradiol was associated with better spatial memory consolidation (Patel et al., 2022) and that administering estradiol in low-estradiol phases impacted navigation strategy/flexibility (Joue et al., 2024). However, as noted in individual plots in Figure 12, the lack of a relationship could be in part due to missing the ovulatory window in some women, as estradiol was actually lower in the ovulatory window than the

early follicular phase in a subset of participants (though it is to be noted the same pattern of findings held even when removing these subjects from analyses). Additionally, both the studies referenced either assessed the relationship between high and low estradiol by classifying women into each grouping post hoc (Patel et al., 2022), or directly manipulated estradiol concentrations (Joue et al., 2024), whereas the current study classified women based on cycle phase history first, and confirmed via salivary assessments afterwards.

We did not find any other differences in performance on any other cognitive measure that was included in this study. This was surprising in regards to mental rotation abilities, as other studies have found differential performance across the menstrual cycle (Moody, 1997; Hausmann et al., 2000; McCormick & Teillon, 2001; Maki et al., 2002; Peragine et al., 2020; Hromatko & Tadinac, 2024). However, a significant difference in our measure of mental rotation in the current study is that we removed items from the Vandenberg and Kuse (1978) mental rotation task that contained structural distractors, in order to eliminate alternative analytical strategies that could be used to solve items (Hegarty, 2018; Munns & Hegarty, 2026). We did find that women performed slightly better in the early follicular phase, so there was a non-significant consistency with the referenced work above, but this difference may be amplified when alternative strategies can be employed. While the lack of associations with other measures of cognition are in line with recent findings of a recent meta-analysis conducted on general cognitive abilities and menstrual cycle phase (Jang et al., 2025), it is one of (if not the first) study that examines a wide battery of cognitive measures in a within-subjects study, finding that survey knowledge acquisition is selectively improved in high, relative to low, estradiol phases.

Limitations

While this study is the first of its kind (to our knowledge) to directly measure spatial learning using immersive VR in menstrual cycle phases characterized by high and low estradiol phases, it had a number of limitations. The first is that while we were primarily interested in examining short-term associations of estradiol (and not progesterone) in young women, we excluded the midluteal phase, which has been previously shown in a couple studies to be associated with shifts in navigational strategy (Hussain et al., 2016; Scheuringer & Pletzer, 2017). As the ovulatory window is a very short window when estradiol peaks (Draper et al., 2018), we are also limited in that a subset of our participants actually had lower estradiol concentrations in their estimated ovulatory window phase (see Appendix B for individual line plots). As such, we may not have properly captured the ovulatory window in some women, meaning that the measured associations may be weaker and partially driven by this subset of participants.

Another limitation of this study is that ovarian hormone concentrations were measured via saliva rather than plasma. While assaying progesterone has been found to be reliably measurable in saliva (e.g., Ferrer et al., 2024), estradiol may not be as reliable, especially when concentrations are low (e.g., Tivis et al., 2005). This could have impacted our results, especially in analyses directly measuring continuous estradiol concentrations in women. However, while salivary estradiol concentrations were generally low among participants, we still captured enough of a gradient to confirm cycle phase windows, showing that salivary, less-invasive procedures can still be used for measuring ovarian hormone concentrations.

Finally, we recruited women under very strict conditions – namely, in that they had to be naturally cycling (no hormonal contraceptive use), have regular cycles by actively

tracking their cycle history, and have no history of any endocrine condition or medication use that could influence the menstrual cycle. As briefly noted in the Participants section, less than a third of all women that were screened qualified for the current study, meaning that these results can only generalize to a smaller subset of women.

Future Directions

This study suggests numerous future directions. An important one is to examine multiple facets of spatial navigation – the current study only focused on ability and strategy pertaining to spatial learning after traveling predetermined routes in an immersive VR environment, but future work could examine a combination of other abilities in immersive VR, such as path integration (similar to Brown et al., 2023), distance estimation, map sketching, spatial learning via exploration, and perspective taking. Additionally, future studies could develop an additional immersive VR environment to include women in their midluteal phase, in addition to the early follicular and ovulatory window phases, in order to paint a more holistic picture to how progesterone interacts with estradiol in spatial learning in young women.

Given that more than half of women aged 15-49 in the US were on some form of contraceptive method between 2022 to 2023 (Daniels & Abma, 2025), it is worth investigating impacts of contraceptive use on spatial navigation abilities in young women, which may reflect a biased subset of women in the present study. As Taylor and colleagues (2020) found that natural fluctuations in brain morphology across a menstrual cycle were minimized with the introduction of a progestin-only oral contraceptive in a young woman, it is possible that spatial cognition abilities could also be impacted to some extent.

Contribution

This study examined the short-term differences of estradiol with spatial learning in novel immersive VR environments in women across two different phases of their menstrual cycle. We additionally included a measure of mental rotation and other aspects of cognition, including processing speed, executive function, episodic memory, inhibition, and working memory. Notably, we found that while general cognition and mental rotation did not differ in performance across menstrual cycles, nor did wayfinding performance (measured via efficiency and place-based strategy use), a measure of survey knowledge acquisition after learning a novel environment (onsite pointing) was better in the ovulatory window (characterized by high estradiol) than the early follicular phase (characterized by low estradiol). These findings provide direct insights into the role of estradiol in young women, in that general navigation success (wayfinding/graph knowledge) is not impacted at the short-term, but estradiol may act to improve more sophisticated survey knowledge acquisition and promote the formation of cognitive maps.

IV. Analyzing the Role of Ovarian Hormone Suppression on Navigation Strategy and Ability Using Age-Matched Controls.

The purpose of Chapter IV was to investigate the longer-term associations between ovarian hormone suppression and spatial navigation ability in young, pre-menopausal women. To do this, I took advantage of a treatment for more severe cases of endometriosis, of which involves ovarian hormone suppression in young women via an oral GnRH receptor antagonist. This approach allowed us to tease out the longer-term impacts of ovarian hormone suppression (essentially a chemical simulation of menopause) on navigation ability and strategy and another measure of hippocampal function (episodic memory via a face-name association task), independent of chronological aging, and compared to age-matched controls who were either naturally-cycling or on a progestin-only contraceptive method.

Endometriosis – A Brief Overview

Endometriosis is an endocrine (specifically, estrogen-dependent), chronic inflammatory condition that affects premenopausal women. Alterations in estrogen signaling have been associated with this condition, as estradiol (specifically, overexpression of estrogen receptor [ER] β) promotes ectopic tissue growth, suppresses ER α expression, and inhibits progesterone production in endometrial cells (see Vercellini et al., 2014 for a review). It is generally characterized by the presence of endometrial tissue outside of the uterus, and is most commonly paired with symptoms such as dysmenorrhea (painful menstrual cramps), dyspareunia (genital pain related to intercourse), infertility, and chronic fatigue (Vercellini et al., 2014; Riazi et al., 2015). It is estimated that endometriosis affects about 10% of premenopausal women worldwide, it is not fully understood what causes it, and there is currently no known cure (World Health Organization, 2025).

Diagnosis of endometriosis can be a long and tenuous path, ranging on average 4 to 11 years between onset of symptoms to a successful surgical diagnosis in women (Agarwal et al., 2019). The current gold standard for diagnosing endometriosis is via laparoscopy to visualize endometrial lesions (Allaire et al., 2023), but is invasive and contributes to the significant delay in diagnosis timelines. As a result, the current recommendation is to provide more clinical diagnoses via reported symptoms and non-invasive imaging techniques (Agarwal et al., 2019; Allaire et al., 2023). Treatment of endometriosis ranges on the severity of the symptoms, starting from general pain management techniques (e.g., NSAIDs), to hormonal contraceptive methods such as the combination pill, patch or ring, progestins such as an intra-uterine device (IUD), gonadotropin-releasing hormone (GnRH) analogues to act as a temporary “castration” method (acting as a menopause induction in women), and for severe cases, surgical treatment such as hysterectomy (surgical removal of the uterus), typically accompanied with the removal of the ovaries (World Health Organization, 2025).

The methods for treating endometriosis range in their influence on ovarian hormones. Combination hormonal contraceptives (e.g., ring, pill, patch) have three primary functions, which are to prevent ovulation, thicken cervical mucus, and thin the endometrium (uterine lining) (Blumenthal & Edelman, 2008). This method inhibits the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn decreases the body’s natural production of estrogen and progesterone (Baird & Glasier, 1993). Hormonal IUDs, in contrast, only release the progestin levonorgestrel in small amounts, but have the same primary functions as the combination contraceptive methods (Cleveland Clinic, 2022).

In more severe cases, hormonal contraceptive and pain relief methods are not enough to treat endometriosis symptomology. Given that endometriosis is an estrogen-dependent

endocrine condition, some women will be prescribed an oral GnRH receptor antagonist, which inhibits growth and proliferation of endometrial cells and essentially acts as a chemical induction of menopause for the period of treatment (Rzewuska et al., 2023). In the most severe cases, women may opt for a hysterectomy to remove the uterus and ovaries. However, the latter option is usually considered after other alternatives have been exhausted and for women who are not planning on having children, as it is an invasive procedure and still does not guarantee full symptomatic relief (World Health Organization, 2025).

Ovarian Hormones, Navigation, and Episodic Memory

Sex steroid hormones (particularly, estradiol and progesterone) have been previously associated with behavioral and neural structures associated with navigation, especially in rodent models. This has been particularly true for studies involving the hippocampus (located in the medial temporal lobe [MTL]), which is a particularly critical neural region for spatial navigation, especially in the development of accurate mental maps of environments (O'Keefe & Nadel, 1978; Maguire et al., 2006; Epstein et al., 2017) and use of *place-based strategies*, which are strategies that involve acquired knowledge of an environment more sophisticated than just remembering a previously-traversed path (a *route- or response-based strategy*, which involves egocentric cues and navigating in reference to the self), and is typically accompanied by the use of allocentric cues from an environment (e.g., global landmarks, using cardinal directions).

For example, a classic study found that in female rats, dendritic spine density increased in CA1 hippocampal pyramidal cells in estrous cycles paired with higher estrogen, relative to other phases with lower estrogen or higher progesterone (Woolley & McEwen, 1993). Direct estradiol infusions in the hippocampus in female rats has also been associated

with greater place-based strategy use in a T-maze task, in which the rats relied more on extramaze cues in order to reach a goal location. This was in direct contrast to direct infusions of estradiol in the dorsolateral striatum, where the rats relied more on egocentric cues and response-based strategy use (Zurkovsky et al., 2006). Additionally, greater doses of estradiol have also been generally associated with greater place-based strategy use in ovariectomized female rats, whereas lower doses have been associated with greater response-based strategy use (Quinlan et al., 2008), and estradiol promotes place-based, but hurts response-based, learning in a plus-maze task (Korol & Kolo, 2002). In contrast, progesterone has been linked to opposing impacts on spatial navigation in rodent studies, with progesterone administration biasing rats towards response-based strategy use in a T-maze task (Lacasse et al., 2022), though this reversal/bias seems to only occur when estradiol is present (Gomez-Perales & Brake, 2023). In sum, rodent studies suggest that navigation strategy may be shaped by dynamic hormonal interactions, rather than the independent effects of a single hormone in naturalistic settings.

Research on ovarian hormones and navigation in women, however, is more sparse and findings are more mixed (in part because pure lesion studies cannot be reliably conducted on humans). For example, one study found that estradiol benefits spatial memory consolidation, in that young women with higher concentrations of estradiol performed better in a virtual Morris Water Maze (indicated by shorter distances traveling to a hidden platform) a day after initially learning the task than women with lower concentrations of estradiol (Patel et al., 2022). Another found that while women in their late follicular/periovulatory window were generally worse in path integration abilities than women in their early follicular

and mid-luteal phases, they performed better when a salient distal landmark was introduced in the task (Brown et al., 2023), indicating better performance with allocentric cue use.

On the other end, another study found that high estradiol phases (i.e., the ovulatory window) was associated with better verbal ability relative to other phases, but lower place-based strategy use than women in their early follicular (when ovarian hormones are low) or midluteal (when estradiol is moderate and progesterone is high) phases (Hussain et al., 2016). It has also been proposed that estradiol may impact navigation flexibility, rather than overall spatial ability, as oral administration of estradiol in women only improved spatial orientation in a virtual, circular arena task (Joue et al., 2024).

However, even less work has been conducted when considering the drastic reduction of ovarian hormones on measures of hippocampal function, such as episodic memory and navigation. One study found that midlife women who were postmenopausal (i.e., a phase characterized by drastic reduction of ovarian hormones and the absence of menstrual cycles) demonstrated greater alterations in hippocampal connectivity and worse performance in episodic memory tasks (the Face Name Associative Memory Exam [FNAME] and Selective Reminding Test [SRT]) than their pre- and peri-menopausal, similarly-aged counterparts (Jacobs et al., 2016). While some preliminary work found that navigation strategy is also impacted as early as midlife (Yu et al., 2021) and this shift seems to be directly related to the natural onset of menopause in midlife women (Yu et al., 2023), no work has directly examined the impacts of ovarian hormone suppression on navigation ability and strategy, or general measures of hippocampal function, in otherwise young women. This is particularly surprising, given that some work has previously shown that the removal of the ovaries and fallopian tubes, prior to the natural onset of menopause, is directly associated with greater

MTL degeneration (which houses the hippocampus) over time than women who naturally experience menopause (Zeydan et al., 2019).

Current Study

As some young women with endometriosis opt to chemically- or surgically-undergo menopause as a treatment for their symptoms, it is important to understand their long-term implications on behavioral measures of hippocampal function, including spatial navigation and episodic memory performance. In this study, we measured spatial navigation and episodic memory (via a face-name associative memory task) in two groups of participants at two different time points. The first group was young, pre-menopausal adult women with a current endometriosis diagnosis, both before and after 3 months of chemically-induced ovarian hormone suppression via an oral drug, Elagolix, which is a GnRH receptor antagonist (thus referred to as *Cases*). The second group was similarly-aged, healthy women that were either naturally-cycling or on a progestin-only contraceptive throughout the course of 3 months, used as a Control condition.

Aside from behavioral measures, we included serum assessments of ovarian hormone concentrations (estradiol and progesterone) in both sessions to act as a manipulation check of hormone changes between the baseline and follow-up visits. As women with endometriosis commonly report chronic pain as a symptom of their condition (World Health Organization, 2025), and chronic pain has been associated with impairments in cognitive function (see Patel et al., 2025 for a review), we included a measure of chronic pain in analyses with spatial navigation performance at baseline, as well as endometriosis-specific pain in Case participants at both the baseline and follow-up visits.

First, we anticipate that regardless Cases and Controls will demonstrate similar wayfinding performance (via efficiency and shortcutting use) at Baseline (as this was prior to Cases undergoing treatment) and they were age-matched. However, our primary hypothesis is that, when ovarian hormones are chemically suppressed in Cases after 3 months (T3), the dramatic decrease of naturally cycling estradiol will result in poorer performance in navigation at T3 and decrease the use of place/shortcutting strategies after learning an environment relative to their Control counterparts. Finally, as we anticipated some practice effects between BL and T3 (Boone et al., 2019), it is hypothesized that Controls will exhibit greater increases in wayfinding performance (demonstrated via better efficiency and more shortcutting use), than Cases between BL and T3 due to the dramatic suppression of estradiol production in Cases (Yu et al., 2023).

Aside from the central hypothesis above, we additionally included chronic pain as a covariate in analyses at BL wayfinding performance, as differences between groups could exist at BL due to Cases potentially having cognitive ability at least partially inhibited via the presence of chronic pain (Patel et al., 2025). We also examined whether estradiol and progesterone were 1) different between the two groups at BL (as women with endometriosis can experience “estrogen dominance,” or elevated levels of $ER\beta$ relative to $ER\alpha$ progesterone, Chantalat et al., 2020) and 2) whether these differences were associated with wayfinding efficiency or shortcutting use. Finally, we additionally assessed whether spatial learning performance was associated with an episodic memory measure (the Face-Name Associative Memory Task [FNAME]), as both abilities are assumed to be metrics of hippocampal function (Amariglio et al., 2012; Lisman et al., 2017), and assessed whether

episodic memory followed a similar pattern of results with ovarian hormone suppression as spatial navigation.

Method

Participants

Adult, pre-menopausal women were recruited to participate in the study at two separate time points, 3 months apart from each other. *Controls* are defined as women that are either naturally cycling or are on progestin-only contraceptive methods (PC). For Control participants, cycle phases are time-locked across sessions, specifically within the early follicular phase (menses) of the cycle. *Cases* are defined as women that are currently diagnosed with endometriosis, and have agreed to take an oral medication, Elagolix, a GnRH receptor antagonist, to treat their condition over the course of 3 months (leading to a chemical induction of ovarian hormone suppression). Participants were age-matched as closely as possible in recruitment procedures.

Baseline (BL) Only

One hundred and fifty-eight participants were recruited in total to participate in the full study, with 88 participants recruited as Control participants and 70 Case participants. Of these participants, only 73 participants completed the Baseline (BL) visit's outcome measures of interest in their entirety. Of these participants, 42 were Controls (ages 18-40, $M = 27.26$ years), and 31 were Cases (ages 19-48, $M = 28.52$ years). Of the Controls, 22 participants were naturally-cycling and 20 participants were on some form of progestin-only contraceptive method (5 with an arm implant, 15 with an intra-uterine device [IUD]).

Both BL and T3

There was a total of 46 participants with usable data across both the BL and 3-month follow-up (T3) sessions, of which 25 were Controls, and 21 were Cases. Of the Controls, 9 participants with both sessions completed were naturally-cycling and 16 were on some form of progestin-only contraceptive method (5 with an arm implant, 11 with an IUD).

4.1.2 Materials

In each session; participants were administered a one-item Chronic Pain Scale sliding measure (higher values mean greater chronic pain), that was only displayed if they indicated currently experiencing chronic pain, and Cases completed the Other tasks were included as part of a larger study, but will not be reported here. The list of additional tasks is noted in Appendix C.

Measure of Navigation Ability. Both the red brick and grey wall versions of the 55x55m desktop DSP (modified from Boone et al., 2018) were administered in this study. In this study, the learning and wayfinding phases are identical to those outlined in the desktop DSP description in Chapter II, as are the outcome measures outlined in Chapters II and III (wayfinding excess distance and solution index [SI] for shortcutting strategies).

Measure of Episodic Memory. The Short Face-Name Associate Memory Task (FNAME, Papp et al., 2014, modified from Rentz et al., 2011) was administered to assess episodic memory. In this task, there are 12 face-name pairs and 12 face-occupation pairs. Participants must remember the face-name associations, face-occupation associations, and finally the face-name-occupation associations for both immediate and delayed recall. In this version there are two initial recall phases (each consisting of 12 face-name pairs and 12 face-occupation pairs), and one cued/delayed recall phase (with 12 face-name and 12 face-occupation pairs). There are a total of 72 items across both initial and delayed recall sessions

(48 in the initial, 24 in the delayed recall), and a higher score indicates better episodic memory performance.

Hormone Analysis. Sex steroid hormone levels and related endocrine markers were collected via fasting, intravenous blood draws from a licensed phlebotomist. The hormones analyzed in this study include serum estradiol (pg/mL) and progesterone (ng/mL).

One 10 mL blood sample was collected in a vacutainer SST (BD Diagnostic Systems) at each session. The sample clotted at room temperature for 45 minutes until being centrifuged (2000×g for 10 min) and serum was then aliquoted into 1 mL microtubes. Serum samples were stored at -80 °C until assayed. Serum concentrations were determined via liquid chromatography mass-spectrometry (for all steroid hormones) at the Brigham and Women's Hospital Research Assay Core. Assay sensitivities, dynamic range, and intra-assay coefficients of variation (respectively) were as follows: estradiol, 1 pg/mL, 1–500 pg/mL, < 5% relative standard deviation (RSD); progesterone, 0.05 ng/mL, 0.05-10 ng/mL, 9.33% RSD. Progesterone values < 0.05 were set at 0.05.

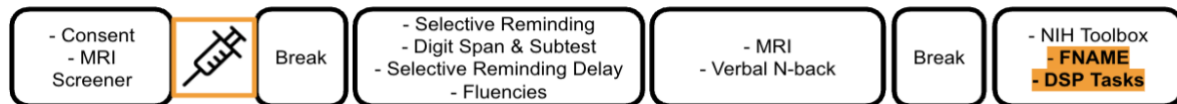
Procedure

Before coming to a lab to participate, participants were contacted via phone interview for an eligibility screening. For participants determined as eligible, they filled out the informed consent via a DocuSign either over the phone or in-person, and completed the questionnaires (all except the Video Game Experience questionnaire) online, on their own time. On the night before participating, participants were asked to fast until being provided breakfast the next morning. The following morning, participants came into the lab and filled out an MRI pre-screening form, followed by a blood draw. Immediately afterwards, they were provided breakfast and then completed the Selective Reminding Task, Digit Span, Digit

Span Subtest, Selective Reminding Task Delayed Recall, and Fluencies tasks. Afterwards, they were escorted to the MRI room for scanning, and completed the N-back task during this scan. After the MRI was completed, participants were provided a lunch break.

When the lunch break concluded, participants were escorted back to the original lab room and completed the NIH Cognitive Toolbox tasks, followed by FNAME, then the red brick DSP tasks (learning, wayfinding, and offsite pointing). Participants were thanked for their time, and paid for their visit (see Figure 16 for a graphical representation of the procedure). They also scheduled their follow-up visit, roughly 3 months after the conclusion of this visit.

Figure 16. Procedure Outline for the Study (with measured variables highlighted in orange).



Roughly one month and 2 months after the conclusion of the first lab visit, participants completed the same series of questionnaires that they responded to before their first session. After roughly 3 months from the initial visit, participants came back to the lab and completed the same tasks as in session 1, with the primary differences being that they did not complete another informed consent or medical history questionnaire, blood draws did not include DNA collection, and participants were administered the grey wall DSP environment (with the same outcome measures). Once they were finished with the follow-up visit, participants were thanked for their time once more and paid for their time.

Analysis Plan

Participants excluded were those who: 1) experienced extreme motion sickness during the DSP, and opted out of completing the tasks, 2) did not complete the second

session, 3) were not compliant in their respective groupings (e.g., changing oral contraceptive use, were not naturally cycling for the full 3 months, or Cases who opted out of taking the Elagolix before the 3 months concluded), and 4) were identified as extreme outliers on a measure (> 3 SDs). For hormone analyses, estradiol and progesterone data points were excluded if they exceeded 3 SDs from the average centered concentration of subjects.

Measures of wayfinding efficiency and SI in the DSP were calculated in the same fashion as Chapters II and III. The FNAME (i.e., the episodic memory measure) is calculated as the correct number of associations made per phase (a total possible score of up to 48 across two initial recall phases, and a total possible score of up to 24 for the delayed recall phase), for a total possible score of up to 72 correct associations. Questionnaires were calculated based on their average score, when taking into account possible reverse-coding.

Manipulation Checks. Manipulation checks include: 1) examining differences in ovarian hormone concentrations (estradiol and progesterone) between Cases and Controls at each visit (BL and T3) via a series independent samples t-tests, 2) comparing wayfinding excess distance and SI between Controls that were either naturally-cycling or on a progestin-only contraceptive at BL via independent samples t-tests, and 3) examining wayfinding excess distance and SI performance in Controls at BL that completed either an older or newer version of the desktop DSP via independent samples t-tests.

Baseline (BL) Only. We first compared wayfinding (excess distance and SI) and FNAME performance between Cases and Controls at BL via a series of independent samples t-tests. Additionally, we measured the Spearman correlation between general chronic pain and navigation (wayfinding excess distance and SI), as well as an independent samples t-test to measure baseline differences in chronic pain levels between Controls and Cases. We

included chronic pain at Baseline as a covariate in an ANCOVA with wayfinding efficiency and SI between the two groups. Finally, we used Pearson's correlations to examine if estradiol and progesterone was generally correlated to navigation performance, regardless of condition.

Both BL & T3. Analyses include 2x2 mixed ANOVAs, where the between-subjects independent variable is the group (Case or Control), and the within-subjects independent variable is the timepoint (baseline and the 3-month follow-up). The dependent variables were wayfinding SI (to assess place vs. response-based strategy use), wayfinding efficiency (via an excess distance metric), and episodic memory/FNAME correct associations made across the initial and delayed recall sessions.

Results

Manipulation Checks

Baseline Hormones. First, we conducted independent samples t-tests to determine if ovarian hormone concentrations (estradiol and progesterone) significantly differed between Cases and Controls. At baseline (BL), estradiol concentrations (pg/mL) did not significantly differ between Controls and Cases, $t(70.94) = -0.43, p = .666$ (see Table 6). Additionally, progesterone concentrations (ng/mL) were not significantly different between Controls ($M = 1.71, SD = 4.60$) and Cases ($M = 1.14, SD = 2.21$) at BL, $t(62.38) = -0.71, p = .482$.

Follow-up Hormones. For the follow-up (T3) visit, however, we anticipated that Cases' ovarian hormone concentrations would be significantly lower relative to their BL visit, and in consequence significantly lower than their Control counterparts. Additionally, we did not anticipate any significant differences in ovarian hormone concentrations in Controls between BL and T3. Descriptive statistics for hormone concentrations are listed in

Table 6. We conducted 2x2 mixed ANOVAs, examining estradiol and progesterone concentrations as the dependent variable, group as the between-subjects independent variable, and timepoint as the within-subjects independent variable. For estradiol, results showed a main effect of group, $F(1,44) = 7.94, p = .007$. There was no significant main effect of timepoint, $F(1,44) = 0.73, p = .398$, and only a marginally significant interaction, $F(1,44) = 2.71, p = .107$, see Figure 17A for an interaction plot. However, when only analyzing Case participants, there was a significant decrease in estradiol concentrations between the BL and T3 visits, $t(20) = 2.53, p = .01$. In summary, Cases overall had lower estradiol concentrations than Controls, but there was no significant difference in timepoint nor interaction. However, this lack of an interaction is likely driven by small sample size.

Table 6. Descriptive Statistics of Estradiol and Progesterone Concentrations in Cases and Controls at the Baseline and Follow-up Visits.

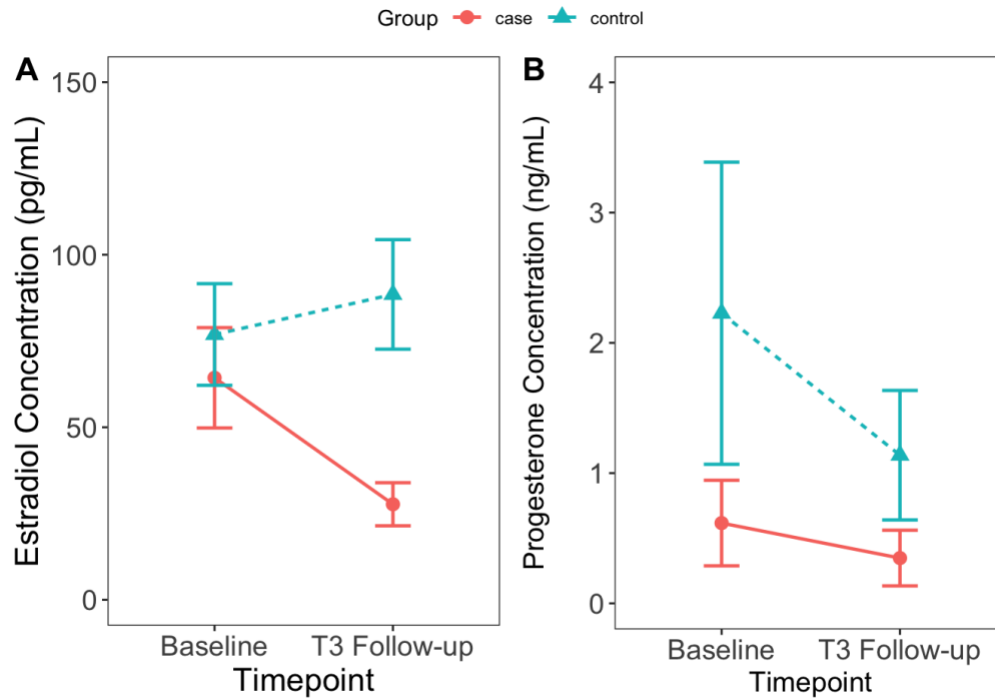
<i>Group</i>	<i>Estradiol (pg/mL)</i>		<i>Progesterone (ng/mL)</i>	
	<i>Baseline</i>	<i>Follow-up</i>	<i>Baseline</i>	<i>Follow-up</i>
Case	69.06 (61.80)	26.82 (28.21)	1.14 (2.21)	0.33 (0.96)
Control	76.35 (81.74)	86.77 (78.26)	1.71 (4.6)	1.10 (2.44)

For progesterone, the 2x2 mixed ANOVA revealed no significant main effect of group, $F(1,44) = 2.08, p = .156$, nor timepoint, $F(1,44) = 1.43, p = .238$, nor interaction between the two, $F(1,44) = 0.52, p = .474$, see Figure 17B. In sum, contrary to expectations, progesterone did not significantly differ between groups or timepoint, and there was no significant interaction.

Endometriosis-Specific Pain. We additionally examined whether the treatment for Cases (via a GnRH receptor antagonist, Elagolix), successfully minimized endometriosis-specific pain after 3 months of ovarian hormone suppression. We did indeed find that Cases

reported significantly less endometriosis-specific pain at the T3 follow-up visit ($M = 32.95$, $SD = 29.99$) than their Baseline visit ($M = 54.26$, $SD = 15.72$), $t(15) = 3.55$, $p = .001$. In sum, the manipulation was overall successful in decreasing Cases' endometriosis-specific pain between the BL and T3 visits.

Figure 17. Interaction Plot for Estradiol (pg/mL) and Progesterone (ng/mL) concentrations between Cases and Controls at Baseline and Follow-up.



Control Participants. We additionally examined whether wayfinding performance (excess distance and SI) differed between Controls at BL, as they differed by being either naturally-cycling or on a progestin-only contraceptive method. Independent samples t-tests revealed that wayfinding excess distance did not significantly differ between naturally-cycling ($M = 0.92$, $SD = 0.22$) and progestin-only contraceptive ($M = 0.92$, $SD = 0.15$) Controls, $t(36.84) = -0.001$, $p = .99$. Similarly, SI also did not significantly differ between

naturally-cycling ($M = 0.34$, $SD = 0.20$) and progestin-only contraceptive ($M = 0.34$, $SD = 0.15$) Controls, $t(39.13) = -0.03$, $p = .977$. In sum, we found no significant differences in performance between naturally-cycling and progestin-only contraceptive Control participants, so we aggregated them in analyses.

DSP Environments. Due to the long time-scale of the study, the DSP maze environments were updated in the midst of data collection in order to decrease motion sickness rates in participants (by slowing the movement speed and changing the mouse sensitivity). We first sought to compare performance between the older and newer versions of the DSP in Control participants at BL, anticipating no significant differences in wayfinding excess distance nor SI between versions. A two-tailed independent samples t-test revealed that Control's BL wayfinding excess distance in the old DSP ($N = 29$, $M = 0.91$, $SD = 0.19$) was not significantly different from Control's BL wayfinding excess distance in the new DSP ($N = 18$, $M = 0.92$, $SD = 0.20$), $t(34.89) = 0.15$, $p = .879$. We found similar findings with SI, in that the old DSP ($M = 0.35$, $SD = 0.17$) did not significantly differ from the new DSP ($M = 0.33$, $SD = 0.19$), $t(32.51) = -0.37$, $p = .712$. Therefore, we included both versions in analyses.

Baseline (BL) Only

We expected no significant differences in performance between Cases and Controls in any of the behavioral measures at BL, as this is before Cases underwent chemically-induced ovarian hormone suppression. Descriptive statistics of wayfinding performance at BL in both groups is noted in Table 7. To test this hypothesis, we conducted two-tailed independent samples t-tests between Controls and Cases in wayfinding excess distance and SI. Contrary to hypotheses, BL Controls' wayfinding excess distance performance was

significantly better than BL Cases' wayfinding excess distance performance, $t(59.64) = 5.54$, $p < .001$ (see Figure 18A). The same results emerged for SI, where Control participants took significantly more shortcuts than Cases, $t(70.97) = -2.29$, $p = .025$ (see Figure 18B). In sum, Control participants generally had better performance than Case participants.

Table 7. Baseline Descriptive Statistics for Controls and Cases in Wayfinding Performance.

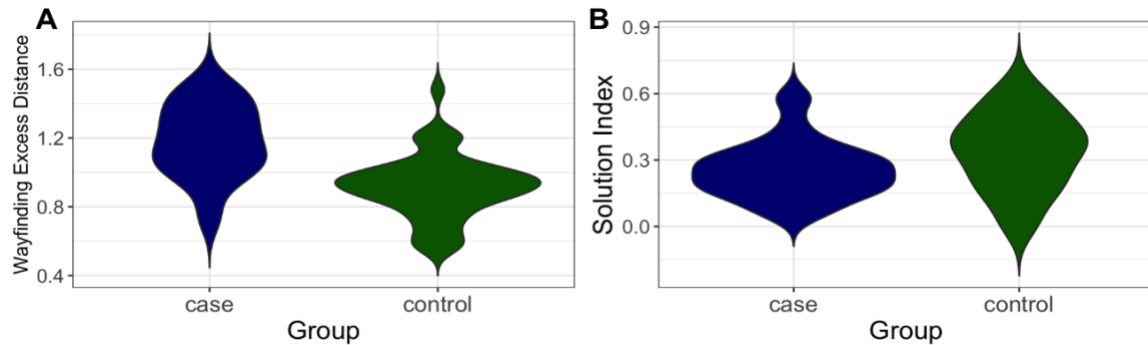
<i>Variable</i>	<i>N</i>	<i>Excess Distance</i>	<i>Excess Distance</i>	<i>Solution Index</i>	<i>Solution Index</i>
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Controls	42	0.92	0.19	0.34	0.17
Cases	31	1.18	0.21	0.26	0.13

Note: Higher values for excess distance indicate worse performance, whereas higher values for solution index indicate more place-based/shortcutting use in wayfinding.

Additionally, we analyzed endometriosis-specific and chronic pain at BL to determine if these differences between groups could be attributable to symptoms of having endometriosis. Endometriosis-specific pain in Case participants at Baseline was not correlated to performance in either wayfinding excess distance, $r(28) = -0.21$, $p = .267$, nor SI, $r(28) = 0.25$, $p = .192$. Cases reported significantly greater chronic pain levels ($M = 3.07$, $SD = 3.08$) than Controls ($M = 0.12$, $SD = 0.79$), $t(32.96) = 5.21$, $p < .001$. Spearman correlation analyses additionally revealed that chronic pain was significantly associated with less wayfinding excess distance, $r(71) = 0.33$, $p = .004$, but was not significantly correlated with SI (navigation strategy), $r(71) = 0.06$, $p = .629$. Interestingly, when only examining the association between chronic pain and spatial learning in Case participants, the opposite patterns emerged – chronic pain was no longer significantly associated with wayfinding excess distance, $r(29) = -0.24$, $p = .187$, but chronic pain was positively associated with SI, $r(29) = 0.58$, $p = .001$. While unexpected, this could in part be due to floor effects in

performance of the participants, as the average SI among participants was lower (see Table 7).

Figure 18. Violin Plots for Wayfinding Excess Distance (A) and Solution Index (B) Between Cases and Controls at Baseline (BL).



We conducted one-way ANCOVAs to determine if original differences between groups at BL in wayfinding metrics still persisted when including chronic pain as a covariate. Results indicated that wayfinding efficiency did not significantly differ between Controls and Cases at Baseline when chronic pain was included as a covariate, $F(1,69) = 0.30, p = .585$, and neither did SI, $F(1,69) = 0.48, p = .490$. In sum, when controlling for chronic pain at BL, Controls and Cases did not significantly differ in wayfinding performance.

As we found that there were no significant group differences in ovarian hormone concentrations, we conducted correlation analyses to determine if estradiol and progesterone were correlated with navigation performance. Estradiol was not significantly correlated with wayfinding efficiency, $r(71) = -0.17, p = .163$, nor SI/shortcut use, $r(71) = -0.13, p = .896$. Progesterone additionally was not significantly correlated with wayfinding efficiency, $r(71) = -0.03, p = .791$, nor SI/shortcut use, $r(71) = -0.13, p = .260$. In sum, we found no significant relations between ovarian hormone concentrations (estradiol or progesterone) and the variables of interest (group, wayfinding excess distance, SI) at Baseline.

Finally, we examined how behavioral measures of hippocampal function (navigation via wayfinding excess distance and SI, and episodic memory via the FNAME) related to each other at Baseline, and if FNAME performance also exhibited differences between Controls and Cases. Using Pearson's correlations, episodic memory (FNAME) total score was not significantly correlated with wayfinding efficiency, $r(69) = -0.18, p = .127$, nor SI/shortcut use, $r(69) = -0.01, p = .905$. These same patterns held, even when breaking results into the initial recall and cued/delayed recall sections of the FNAME. Additionally, an independent samples t-test revealed no significant differences in the total FNAME score between Controls ($M = 53.17, SD = 9.67$) and Cases ($M = 49.21, SD = 11.08$) at BL, $t(54.83) = -1.56, p = .125$. In sum, we found no significant associations between episodic memory and navigation performance at BL, nor significant differences in episodic memory performance between Controls and Cases at BL.

Both BL & T3

By the 3-month follow-up (T3), it was hypothesized that Controls would exhibit better wayfinding performance than Cases, both in wayfinding efficiency (i.e., less excess distance) and greater use of shortcutting strategies (SI), due to Cases having estradiol production clinically suppressed between BL and T3. Finally, as we anticipated there to be at least some practice effect between BL and T3, it was hypothesized that Controls would exhibit a greater increase in wayfinding performance than Cases. Descriptive statistics of wayfinding excess distance and solution index across the two groups are noted in Table 8. To test this hypothesis, we conducted 2x2 mixed ANOVAs with one between-subjects independent variable (participant group – Control or Case) and one within-subjects independent variable (timepoint – BL or T3). For wayfinding efficiency, we found a

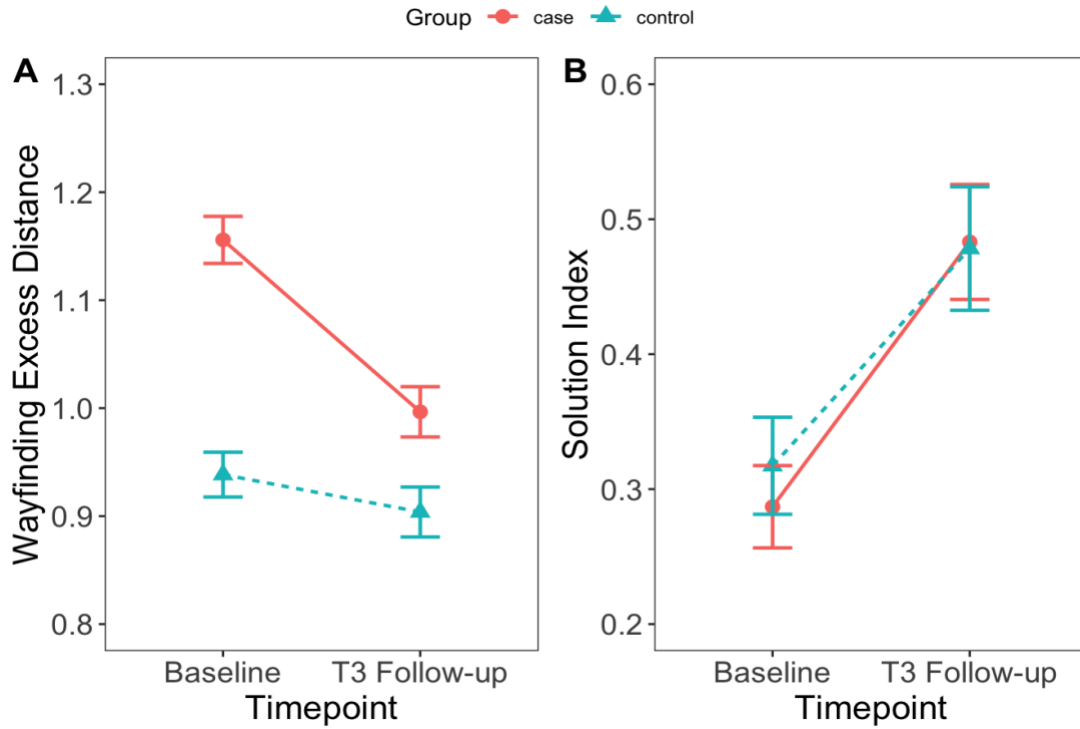
significant main effect of Group, $F(1,44) = 8.67, p = .005$, as well as a significant main effect of Timepoint, $F(1,44) = 7.77, p = .008$. While not significant, we found a marginal interaction between Group and Timepoint, $F(1,44) = 3.21, p = .080$. Controls were generally more efficient/had lower excess distance than Cases, and both groups significantly improved in efficiency between BL and T3. While the interaction was not significant, trends indicate that Cases demonstrate slightly more improvement over time than Controls (see Figure 19A).

Table 8. T3 Descriptive Statistics for Controls and Cases in Wayfinding Performance.

<i>Variable</i>	<i>N</i>	<i>Excess Distance</i>		<i>Solution Index</i>	
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Controls	25	0.92	0.21	0.40	0.22
Cases	21	1.08	0.23	0.39	0.19

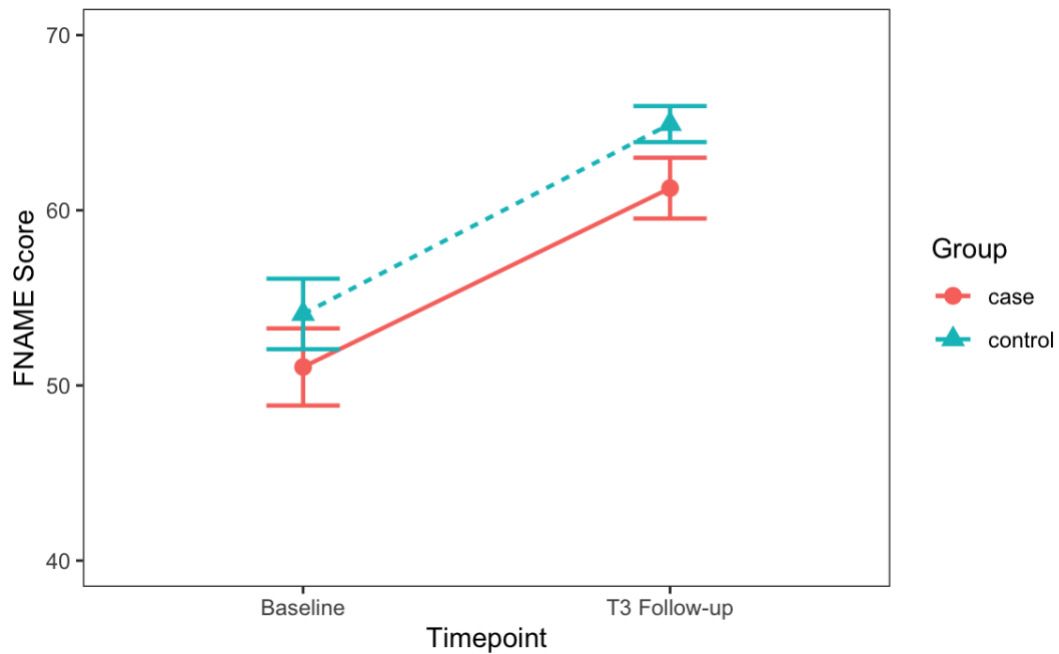
For SI/shortcutting strategy use, we only found a significant main effect of timepoint, $F(1,44) = 33.84, p < .001$. We did not find a significant main effect of group, $F(1,44) = 0.07, p = .789$, nor a significant interaction, $F(1,44) = 0.33, p = .569$. For SI/shortcutting behaviors in wayfinding, both groups took more shortcuts in the T3/follow-up visit than at Baseline (see Figure 19B). In sum, our hypothesis was not supported – while Control participants did improve over the two sessions, Cases also demonstrated improvements (and in the case of wayfinding efficiency/excess distance, slightly more so than their Control counterparts).

Figure 19. Interaction Plots for Wayfinding Excess Distance (A) and Solution Index (B) Between Cases and Controls at BL and T3.



. To examine the FNAME data, we employed a 2x2 mixed ANOVA with group (Control or Case) as the between-subjects independent variable and timepoint (BL or T3) as the within-subjects independent variable. Results revealed no significant main effect of group, $F = 2.56, p = .117$. However, there was a significant main effect of timepoint, such that both groups improved in performance between BL ($M = 52.77, SD = 9.87$) and T3 ($M = 63.34, SD = 6.48$), $F(1,42) = 55.83, p < .001$. There was no significant interaction between group and timepoint, $F(1,42) = 0.05, p = .824$ (see Figure 20). In sum, we found that regardless of group, everyone performed better in the FNAME by the follow-up (T3) session compared to Baseline, but there were no other significant differences or interaction effects.

Figure 20. Interaction Plot for FNAME Performance Between Cases and Controls at BL and T3.



Finally, we examined endometriosis-specific pain in Case participants at T3 with wayfinding efficiency and solution index/shortcutting strategy use. As with the BL visit, endometriosis-specific pain was not significantly correlated with wayfinding excess distance, $r(15) = -0.05$, $p = .863$, nor solution index, $r(15) = -0.12$, $p = .647$. In sum, endometriosis-specific pain did not significantly impact any of the wayfinding measures.

4.4 Discussion

This chapter examined the impacts of ovarian hormone suppression on navigation. In this study, young women (Cases) were tested on their ability to find their way to objects after learning their locations in a desktop environment both before (Baseline, BL) and after undergoing chemically-induced ovarian hormone suppression via a GnRH receptor antagonist for 3 months (Follow-up, T3). We compared their performance (via wayfinding efficiency and navigational strategy use) to similarly-aged Control participants who were

either naturally-cycling or on a progestin-only contraceptive method (as Control participants, naturally-cycling or on a progestin-only contraceptive, did not significantly differ in performance from one another).

Contrary to our initial expectations, Control participants were both more efficient and utilized more shortcuts in wayfinding than Cases at the BL visit, despite this session being prior to Cases undergoing ovarian hormone suppression, and despite not finding any significant differences in ovarian hormone concentrations between the groups at this timepoint (nor any significant associations between ovarian hormones and wayfinding performance). However, as all Case participants consisted of women with a current endometriosis diagnosis, and they were about to undergo ovarian hormone suppression as a treatment for this condition, this difference could have been due to chronic pain (a common symptom of endometriosis, Vercellini et al., 2014; Riazi et al., 2015). Indeed, we found that chronic pain was significantly positively correlated with greater excess distance in wayfinding, and when chronic pain was included as a covariate, wayfinding performance did not significantly differ between groups at Baseline.

Interestingly, we found that episodic memory performance as measured by the Face-Name Associative Memory task, another measure of hippocampal function (Rentz et al., 2011; Amariglio et al., 2012), was not significantly different between Control and Case participants at Baseline. While this is in line with expectations that behavioral performance would not significantly differ between groups at the BL visit, it is a finding that is in direct contrast to our results with wayfinding efficiency and shortcutting strategies (prior to controlling for chronic pain). This is particularly surprising, given that episodic memory and navigation performance are assumed to rely on similar encoding systems in the hippocampus,

and at least be partially related, even if they are only somewhat dissociated (Buzsaki & Moser, 2013; Nguyen et al., 2025). However, we could not replicate this association in this study. As such, it is possible that wayfinding performance is more selectively impacted by chronic pain (or general chronic fatigue) than face-name associations, possibly because spatial learning and wayfinding are more challenging than remembering face-name and face-occupation pairings.

At the follow-up visit (T3), we hypothesized that Cases would demonstrate worse navigation efficiency and less use of shortcutting strategies in wayfinding relative to their Control counterparts, due to Cases' clinical suppression of estradiol since the Baseline visit. While we did find that Cases had worse wayfinding efficiency performance than Controls, shortcutting use in wayfinding did not significantly differ between groups at T3. Even more surprising, and contrary to original hypotheses, Case participants significantly improved in their wayfinding efficiency, marginally more so than their Control counterparts between the BL and T3 visits. Additionally, episodic memory performance generally increased across both groups between BL and T3, and Controls had slightly better performance than Cases. This result has a few possible explanations. The first is that there are other symptoms related to endometriosis that result in greater detriments to spatial learning abilities (e.g., chronic pain), and the absence of these symptoms result in greater improvements in ability than any possible detriments of ovarian hormone suppression. The other is that, given that both groups improved in performance by the follow-up session, there was generally more room for improvement in Case participants than in Controls.

Limitations

While this study presents novel findings to ovarian hormone suppression's impacts (or lack thereof) on spatial learning performance, there are limitations in the conclusions that can be made. First, the major limitation is the sample size we were able to achieve in the study. By the follow-up visit we were only able to collect about 20 participants in each group, and the effects of ovarian hormone suppression on navigation abilities may be smaller than what we could detect in our dataset. Additionally, the presence of endometriosis symptoms such as chronic pain at the Baseline visit, could result in substantial general differences in cognitive performance as could the methods being used to alleviate symptoms prior to the introduction of the GnRH receptor antagonist (e.g., contraceptive methods that were not controlled for in recruitment procedures). The alleviation of these symptoms may result in better overall performance over time than any potential detriments of ovarian hormone suppression, which could have nullified results. Because of these confounds, we could not isolate the nature of how ovarian hormone suppression, in otherwise healthy, young, pre-menopausal women, impacts spatial learning. It is to be noted, however, that endometriosis-specific pain was not correlated with any of the spatial learning measures in Cases in the Baseline and Follow-up visits, but this could be primarily a limitation of sample size.

Another limitation was the interface used to measure spatial learning and navigation performance. Due to the nature and timeline of this study, only the desktop environments could be administered to the participants. As such, a significant number of participants across conditions dropped out due to motion sickness, which was seen in Chapter II to also be associated with the desktop version of the task compared to the immersive ambulatory version. Additionally, the DSP tasks were administered at the end of the study (which lasted

approximately 5-6 hours in total for each session), and participants may have experienced more severe motion sickness due to fatigue. This, as a major consequence (and as the major limitation of this study), further limited the sample size we were able to collect, especially from Case participants, who were particularly impacted by motion sickness in the environments (possibly in part from reporting experiencing symptoms of menopause during the course of treatment).

Future Directions

There are a few avenues for future research from this study's findings. The first is to include an immersive, ambulatory spatial learning task to minimize motion sickness and drop-out rates in more sensitive populations, especially in regards to Case participants. Additionally, the inclusion of an immersive interface might allow researchers to study navigation under more naturalistic conditions that include body-based senses, and determine if ovarian hormone suppression has a greater impact on one or the other in spatial knowledge acquisition.

Another future direction, albeit ambitious and likely impossible to conduct due to ethical concerns, is to study impacts of ovarian hormone suppression in non-clinical, healthy populations of young women. This study adopted a convenience sampling approach as women with endometriosis were previously prescribed the GnRH receptor antagonist in order to treat their symptoms, but it did not allow for this research to fully disentangle how ovarian hormone suppression would impact spatial learning in women without this diagnosis. Additionally, it could be that estradiol has a curvilinear relationship with spatial learning and strategy, in that moderate concentrations are associated with better performance, relative to lower or higher concentrations (for example, in endometriosis which can be characterized by

over-production of estrogen). This relationship has been generally found with testosterone concentrations and navigation ability (e.g., Spritzer et al., 2011), and could at least partially explain mixed findings with estradiol and navigation in previous studies examining between-subjects participants (e.g., Hussain et al., 2016; Patel et al., 2022; Brown et al., 2023; Joue et al., 2024).

Contribution

This study examined the longer-term impacts of ovarian hormone suppression on wayfinding efficiency and navigation strategy after learning in a novel, desktop environment. Generally, we found that women with endometriosis were not significantly negatively impacted in performance by 3 months of ovarian hormone suppression as a treatment for their condition, and actually improved over the course of treatment (possibly due to mitigation of chronic pain or greater room for improvement from performance at Baseline). While findings were contrary to most of our expectations and hypotheses, this is one of the first studies of its kind to disentangle loss of ovarian hormones from chronological aging in spatial navigation ability and strategy in women, even if only from the lens of treating endocrine conditions.

V. General Discussion

The study of the endocrine system, especially in regards to women's health and cognitive abilities, has been largely ignored until relatively recently (in the last couple of decades). This is especially true for the study of women's spatial cognition abilities. Despite women having proportionately more estrogen receptors in the hippocampus relative to men and exhibiting differences in hippocampal plasticity and neurogenesis (Yagi & Galea, 2019), and the hippocampus being a critical brain region for spatial navigation and forming metrically accurate cognitive maps (e.g., O'Keefe & Nadel, 1978; Maguire et al., 2006; Byrne et al., 2007; Moser et al., 2008; Ekstrom & Hill, 2023), little work has been devoted to the study of how ovarian hormones shape spatial knowledge acquisition. The study of behavioral sex differences in spatial cognition broadly finds that men tend to outperform women in tasks that require metrically accurate survey knowledge (see Nazareth et al., 2019 for a review), whereas women are comparable to men in tasks related to replicating previously learned routes and better than men in static object-location memory (Silverman & Eals, 1992; New et al., 2007; Voyer et al., 2007).

However, prior literature fails to examine how ovarian hormones may play a driving role in the magnitude of these sex differences. Most young, pre-menopausal women have a menstrual cycle that lasts approximately 28 days on average that includes variation in their ovarian hormone concentrations, such as estradiol and progesterone (Draper et al., 2018). Given that estradiol has been previously shown to increase dendritic spine density in the hippocampus (Wooley & McEwen, 1993), it is possible that estradiol may directly impact spatial knowledge acquisition. Additionally, most women will undergo menopause, or the loss of menstrual cycles (and consequently, the drastic reduction of ovarian hormone concentrations) either around midlife or as a treatment for a chronic endocrine condition

(such as endometriosis), which may be associated with a marked shift in spatial knowledge acquisition ability (Yu et al., 2023), greater cognitive decline over time (Koebele et al., 2017), as well as neurodegeneration in the medial temporal lobe, which houses the hippocampus, that increases with earlier menopause onset (Zeydan et al., 2019).

This dissertation's primary goal was to directly examine effects of ovarian hormones on spatial learning in young, premenopausal women in virtual reality (VR) environments. Chapter II first established the methodology for the study and examined spatial learning in immersive ambulatory and desktop VR environments, with the immersive and small desktop environments developed specifically for the purpose of this dissertation. This chapter consisted of two studies. The first study examined immersive and desktop VR spatial learning within-subjects, with participants completing two maze environments that were identical in procedure and almost identical in structure, differing only to the extent that participants perceived each maze as a different environment (e.g., red brick vs. grey wall, environments being mirror images of each other, and different objects), and via environment size due to the immersive environment being scaled down to fit in a 10 x 10m, room-sized space (whereas the desktop environment was 55 x 55m). The second study in Chapter II examined spatial learning in immersive and desktop VR environments between-subjects, keeping the maze environment exactly the same in structure, and only differing in 1) the interface (immersive ambulatory or desktop), and/or 2) the size of the environment (10 x 10m or 55 x 55m). The general maze environments, structure, and task procedure were consistent across the dissertation, with the exception of Chapter IV (which did not incorporate an onsite pointing task). Additionally, Chapter III only incorporated the

immersive, 10 x 10m versions of the maze environments, whereas Chapter IV only used the desktop, 55 x 55m versions.

For Chapter II I hypothesized that navigation performance after learning objects in a maze, as measured by wayfinding efficiency and onsite pointing error, would be highly correlated across immersive ambulatory and desktop VR interfaces. However, I anticipated that regardless of this association, immersive onsite pointing performance would be better (have less angular error) than desktop onsite pointing performance, as immersive environments allow for body-based proprioceptive and vestibular cues (Ruddle et al., 2011; Anastasiou et al., 2023; De Back et al., 2025). For wayfinding, there were two alternative hypotheses. The first was that body-based cues might enhance survey knowledge specifically (Chrastil & Warren, 2013), and wayfinding may not be improved with the inclusion of body-based cues (Chrastil & Warren, 2015). The second alternative hypothesis was that if wayfinding also depends on a similar level of survey knowledge acquisition (and reflects more of a continuum of the same ability), then we would anticipate performance to follow the same pattern as pointing; namely, that wayfinding in immersive would be better than desktop VR (Anastasiou et al., 2023; De Back et al., 2025). Finally, I examined whether environment size influenced wayfinding and onsite pointing performance, when controlling for interface.

The results from Chapter II revealed that, as expected, pointing and wayfinding performance across immersive and desktop VR interfaces were significantly correlated with each other (as assessed by Study 1). Additionally, both studies in this chapter found that onsite pointing ability was better after learning in an immersive VR environment, than in a desktop one. However, wayfinding efficiency did not significantly differ across interfaces in

both studies, supporting the first alternative hypothesis that is consistent with Chrastil & Warren (2015). These results with pointing and wayfinding held even after controlling for self-reported motion sickness, which was generally worse in the desktop VR interface conditions. Finally, I did not find any evidence that environment size influenced spatial knowledge acquisition, at least in a maze-like environment (as examined by Study 2).

Chapter III examined ovarian hormones and spatial cognition over the menstrual cycle. In this study, naturally, regularly-cycling pre-menopausal women participated at 2 points in their menstrual cycle classified by low estradiol and progesterone (the early follicular phases/menses) and high estradiol but low progesterone (the ovulatory window). Saliva was collected before and after the immersive maze tasks (learning, pointing, wayfinding) to confirm cycle phase, and participants took daily LH tests to confirm the ovulatory window after their menses ended. In addition to immersive VR navigation in each session, participants also completed a 10-item online mental rotation task and a general cognitive battery via the NIH Cognitive Toolbox (tasks measuring processing speed, executive function, working memory, episodic memory, and inhibition). Women were counterbalanced in the cycle phase session order (early follicular or ovulatory window first), and nested counterbalanced in the version order of the maze environment (red brick or grey wall).

For Chapter III it was hypothesized that women in the ovulatory window (high estradiol phase) would have better onsite pointing ability, wayfinding efficiency, and more place-based/shortcutting strategies after learning the locations of objects in an immersive maze than when they were in their early follicular/menses (low estradiol phase). This hypothesis was derived via previous rodent research conducted on female rats, where high

estradiol was associated with greater place-based strategy use (Korol & Kolo, 2002; Zurkovsky et al., 2006; Quinlan et al., 2008) and increased dendritic spine density in the hippocampus (Wooley & McEwen, 1993). In contrast, I hypothesized that mental rotation ability, a small-scale measure of spatial cognition, would be better in the early follicular phase, when estradiol is low, and worse in the ovulatory window (in line with Moody, 1997; Hausmann et al., 2000; McCormick & Teillon, 2001; Maki et al., 2002; Peragine et al., 2020; Hromatko & Tadinac, 2024).

The results from Chapter III demonstrate that very few aspects of spatial cognition are impacted by the variation in estradiol across the menstrual cycle. In this study, only onsite pointing ability was impacted by cycle phase, in that women had better pointing ability (less angular error) in their ovulatory window (high estradiol) than the early follicular phase (low estradiol), providing support for the original hypothesis. However, neither measure of wayfinding (efficiency or place-based strategies) significantly differed across cycle phases, nor did mental rotation or general cognition. Finally, while I did find that pointing was better in the ovulatory window, neither estradiol nor progesterone levels directly predicted any of the navigation outcome measures. As this appears to be the first study that directly addresses menstrual cycle differences in immersive VR navigation abilities, it demonstrates that estradiol alone does not impact wayfinding in highly constrained maze environments, but may improve the quality and fine-tuning of spatial knowledge acquisition. A secondary result of this study is that salivary measurements of estradiol and progesterone can be used to reliably confirm cycle phase windows.

Chapter IV examined ovarian hormones and spatial learning from a longer-term timescale in young women, specifically on the impacts of chemically-inducing menopause

(via an oral GnRH receptor antagonist, Elagolix) for 3 months in women with an endometriosis diagnosis. In this study, women with endometriosis (*Cases*) participated at two different timepoints – once immediately prior to beginning treatment, and once after 3 months of being on the treatment. Using this longitudinal design, I was able to examine how ovarian hormone suppression impacted spatial learning (specifically, via wayfinding efficiency and strategy) in women, independent of chronological aging. Additionally, we included relatively age-matched, healthy young women (who were either naturally-cycling or on a progestin-only contraceptive method) who participated at the same time points to serve as a Control group. Aside from the desktop maze environment to assess spatial learning, a face-name associative memory exam task was also included as a measure of hippocampal function, namely episodic memory performance (Rentz et al., 2011). Serum ovarian hormone assessments were collected via a fasting blood draw in the morning, and the face-name and desktop maze tasks (learning, wayfinding) were assessed in the afternoon, at the end of a larger study protocol.

For Chapter IV it was generally expected that, at the initial (baseline) visit, there would be no significant differences in wayfinding efficiency nor place-based strategy use between Cases (women with endometriosis) and Controls. The main hypothesis was that after 3 months of ovarian hormone suppression, Cases would have impacted navigation performance over time and decrease the use of place-based/shortcutting behaviors after learning objects in a desktop maze environment, relative to their Control counterparts. While I anticipated general practice effects between the baseline visit and 3-month follow up (Boone et al., 2019), I hypothesized that Controls would have greater increases in efficiency and place-based strategy use between the two visits, whereas Cases would have less of this

increase due to ovarian hormones (more specifically, estradiol) being suppressed for 3 months.

The results from Chapter IV were not consistent with our original expectations. At the baseline visit, Control participants were both more efficient in wayfinding and took more shortcuts than Case participants after learning the locations of objects in a desktop maze environment, despite ovarian hormone concentrations not significantly differing between the two groups at baseline. This was likely due to Cases experiencing more chronic pain relative to Controls, which is a common symptom of endometriosis (Vercellini et al., 2014). After controlling for chronic pain, Cases and Controls did not significantly differ in wayfinding performance at baseline. Interestingly, wayfinding efficiency and navigational strategy was not significantly correlated with the face-name associative memory task, and performance in the face-name associative memory exam did not significantly differ between groups at the baseline visit. At the follow-up visit, both groups (Cases and Controls) significantly improved in wayfinding metrics and face-name associative memory from the baseline visit. However, in the case of wayfinding efficiency, Cases demonstrated marginally greater improvements. In summary, women treated for with endometriosis for three months do not experience significant detriments to spatial learning (as measured by wayfinding efficiency and navigational strategy), or general decline in behavioral measures of hippocampal function. In fact it seems to be the opposite – women with endometriosis may potentially benefit from this treatment, as results more seem to indicate that any cognitive deficits associated with chronic pain (Patel et al., 2025) are more alleviated by ovarian hormone suppression than any potential cognitive impairment from ovarian hormone suppression alone.

Limitations and Future Directions

These studies were not without limitations. While Chapter III did find significant differences in pointing ability by cycle phase, the participant sample size was still limited to 31 participants, and only measured two points of the cycle (rather than continuous measurements across all phases. Previous work has found differences in navigational strategy when the midluteal phase (characterized by high estradiol and progesterone) was included (Hussain et al., 2016; Scheuringer & Pletzer, 2017), and progesterone has shown direct impacts on both navigational strategy (Lacasse et al., 2022; Gomez-Perales & Brake, 2023) and morphology of neural structures implicated in navigation (Taylor et al., 2020), it is important for future studies to include this phase to show how progesterone changes impact spatial learning and general spatial knowledge acquisition in immersive environments. Additionally, the women studied in Chapter III were healthy, naturally and regularly cycling young women – as a large proportion of reproductive aged women are on some form of hormonal contraceptive (Daniels & Abma, 2025), a future study can examine to what extent hormonal contraceptives impact spatial learning, as the sample collected in this study may not be representative of all women.

In Chapter IV the Cases were all women with endometriosis – an estrogen-dependent chronic inflammatory condition that is associated with chronic pain and overproduction of estrogen relative to progesterone (Vercellini et al., 2014). This was an approach to begin to understand impacts of ovarian hormone suppression, independently of chronological aging, but is confounded by differences between the Cases and Controls including chronic pain, as well as a limited sample size in the follow-up visit. While this study provides a positive take on treatment for endometriosis, in that it suggests that the benefits of treating chronic pain is

greater than any potential detrimental effects of ovarian hormone suppression on cognitive abilities (and does not force women with endocrine conditions to “pick their battles”), this study could not disentangle ovarian hormone suppression impacts on spatial learning from other general differences in participant characteristics (e.g., chronic pain, the presence of an endocrine condition) in otherwise healthy young women. A future direction could be to study ovarian hormone suppression in healthy, naturally-cycling young women absent of an endocrine condition, although this would be an ambitious undertaking. Additionally, this study did not include a measure of pointing ability, which was more susceptible to ovarian hormone changes from Chapter III, and the tasks were conducted in a desktop virtual environment. Future studies could include multiple measures of spatial learning and navigation (rather than wayfinding alone) and use immersive VR mazes to include body-based cues in learning.

This dissertation primarily focuses on spatial learning after traveling along a guided route in a maze-like environment; however, there are many areas of navigation and general spatial cognition left largely unexplored, including learning via exploration, path integration, perspective taking, route following, and map-based navigation. While spatial learning is most studied in spatial navigation research, future efforts can examine if these other components of spatial navigation are impacted by changes in ovarian hormones.

Implications

A few theoretical implications can be drawn from the studies in this dissertation. The first is that this dissertation provided support for Chrastil and Warren’s previous findings, in that pointing ability is enhanced with the inclusion of body-based cues (2013) and wayfinding is not (2015). While the authors originally attribute this to be a distinction

between graph and survey knowledge, it could also be that both measures are on a continuum of survey knowledge acquisition – the ability to find one’s way in an environment is easier to achieve and does not require body-based cues for success, whereas the ability to point is harder, requires greater precision, and is enhanced with body-based cues. This extended to the broader effects of changes in ovarian hormones across the dissertation, where changes in estradiol did not impact wayfinding in Chapter III nor Chapter IV, but did impact pointing. This suggests that survey knowledge measures that require greater metric precision (e.g., pointing) are more sensitive to detect ovarian hormone impacts on spatial learning. While this comment is purely speculative, it could very well be that we would find a similar result (i.e., pointing ability worsening with ovarian hormone suppression) if a similar onsite pointing measure was included in Chapter IV.

Similarly, from the lens of the menstrual cycle, this dissertation provided the first known evidence that short-term (menstrual cycle) differences in estradiol concentrations directly impact survey knowledge metrics (in that higher estradiol phases show better in survey knowledge), but graph knowledge (or less precise survey knowledge) remains largely intact. This supports the existing theory that estradiol may act as a promoter to hippocampal function (Wooley & McEwen, 1993), in which the hippocampus has been directly linked to survey knowledge acquisition or cognitive map formation (Ekstrom et al., 2023). This distinction also possibly explains why women do not generally notice navigation differences across the menstrual cycle – most everyday navigation can be accomplished with route and graph knowledge, which does not seem to be impacted in these shorter-term timescales.

There are a few possible reasons why changes in estradiol may impact survey knowledge acquisition. First, as the hippocampus contains many estrogen receptors, and

proportionally more in women than men (Yagi & Galea, 2019), there may be some evolved, adaptive mechanism that buffers survey knowledge acquisition abilities in women's reproductive years. While any reason for why estradiol enhances survey knowledge is purely speculative, it could be that estradiol acts as a general "fine-tuner" for naturalistic cognitive tasks involving the hippocampus, such as navigating to find new forageable resources prior to points of conception, when women are less mobile and have to dedicate more resources to pregnancy and carrying a child. However, more research is needed examining the adaptive function of estradiol as it pertains to spatial navigation.

An alternative explanation, that would explain findings from both Chapters III and IV, is that rather than estradiol boosting survey knowledge, the presence of pain acts as a detriment to it. Many women report menstrual cycle pain and cramping in their early follicular/menses phase, and it is quite possible that its presence negatively impacts more fine-tuned, metrically accurate survey knowledge acquisition. Similarly, we found that women with endometriosis (and greater chronic pain) performed significantly worse in wayfinding prior to the treatment of their condition (compared to their Control counterparts), and including chronic pain as a covariate removed this initial difference (but, it is to be noted that endometriosis-specific pain was not associated with wayfinding in this study).

Conclusion

This dissertation takes a novel approach to understanding the nature of ovarian hormone effects on spatial cognition abilities in young women, via the menstrual cycle (shorter-term timescales) and ovarian hormone suppression (menopause/longer-term timescales). In regards to the menstrual cycle, this is the first study (to our knowledge) that examines spatial learning in immersive VR across the menstrual cycle, isolating phases of the

cycle that differ primarily in estradiol concentrations. Additionally, this dissertation contains the first study of its kind to examine a treatment for endometriosis as a proxy for menopause in young women, examining spatial learning independent of chronological aging effects. This work adds another piece to the large puzzle that is understanding women' health and cognitive abilities, providing support that the ability to find your way after learning an environment remains intact in women, resilient to the effects of hormone fluctuations.

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Appendix A

Video Game Experience Questionnaire (Study 1)

1. Have you ever played video games on a regular basis (i.e., consistently or frequently several times a week)?
 - a. Yes (1)
 - b. No (0) → Skip the remaining questionnaire
2. How often (approximately do you currently consistently play video games)?
 - a. 0 hours/week (1)
 - b. 1-5 hours/week (2)
 - c. 5-10 hours/week (3)
 - d. 10-15 hours/week (4)
 - e. 15-20 hours/week (5)
 - f. 20+ hours/week (6)
3. Reflect on your video game experience. In the period of your life that you are/were most active playing video games, what was the average number of hours per week that you spent on playing video games?
 - a. 0 hours/week (1)
 - b. 1-5 hours/week (2)
 - c. 5-10 hours/week (3)
 - d. 10-15 hours/week (4)
 - e. 15-20 hours/week (5)
 - f. 20+ hours/week (6)
4. How many years have/did you consistently play video games across your lifetime (i.e., playing at least monthly)? [*Open-ended response*]
5. How good do you feel you are at playing video games?
 - a. Expert (5)
 - b. Very good (4)
 - c. Moderately good (3)
 - d. Not very skilled (2)
 - e. No skill (1)
6. Approximately how many hours per week do you currently spend playing video games that involve learning the layout of virtual environments (e.g., Halo, Call of Duty, World of Warcraft, Fortnite)?
 - a. 0 hours/week (i.e., I currently do not play these types of video games) (1)
 - b. 1-5 hours/week (2)
 - c. 5-10 hours/week (3)
 - d. 10-15 hours/week (4)
 - e. 15-20 hours/week (5)
 - f. 20+ hours/week (6)

7. Think about the time in your life when you played the most video games that involved learning the layout of virtual environments. How often did you play these types of video games during that time?
 - a. 0 hours/week (i.e., I did not play these types of video games) (1)
 - b. 1-5 hours/week (2)
 - c. 5-10 hours/week (3)
 - d. 10-15 hours/week (4)
 - e. 15-20 hours/week (5)
 - f. 20+ hours/week (6)
8. Think about the time in your life when you played the most video games that involved learning the layout of virtual environments. How long is/was the period that you were most active in playing these types of games?
 - a. 0 months (1)
 - b. 1-12 months (2)
 - c. 1-2 years (3)
 - d. 2-5 years (4)
 - e. 5-10 years (5)
 - f. 10+ years (6)

Modified Video Game Experience Questionnaire (Study 2)

1. Do you currently play video games on a regular basis?
 - a. Yes (1)
 - b. No (0)
2. [If Q1 = “No”] Have you played video games on a regular basis within the last 5 years?
 - a. Yes (1)
 - b. No (0)
3. Do you currently have a device to play video games?
 - a. Yes
 - b. No
4. [If Q3 = “Yes”] What type(s)? [*Open-ended response*]
5. Are you currently in college?
 - a. Yes
 - b. No
6. [If Q5 = “Yes”] How often (approximately) do you consistently play video games while at college?
 - a. Daily (5)
 - b. Weekly (4)
 - c. Monthly (3)

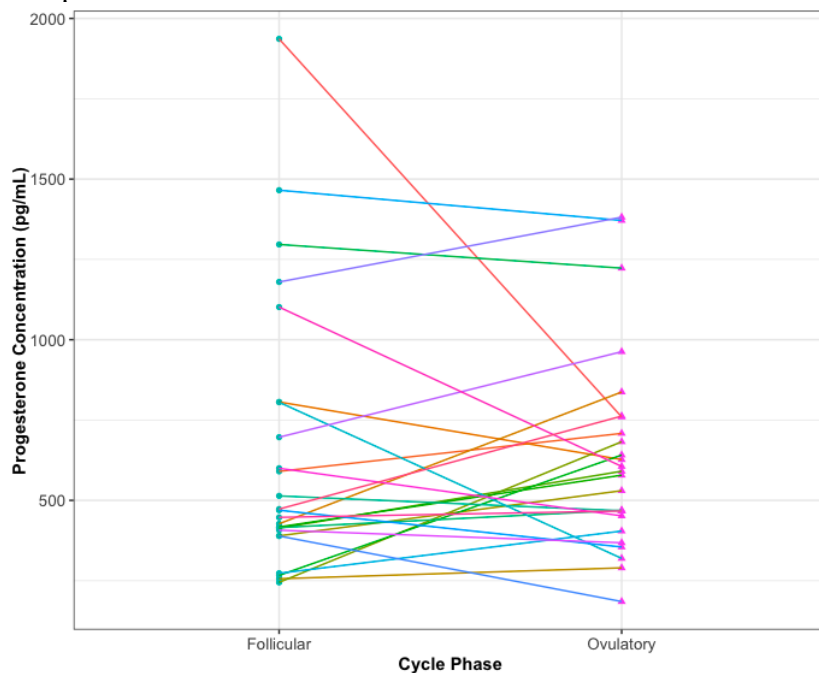
- d. Few times a year (2)
 - e. Never (1)
7. [If Q5 = “Yes”] How often (approximately) do you consistently play video games at home or on break?
- a. Daily (5)
 - b. Weekly (4)
 - c. Monthly (3)
 - d. Few times a year (2)
 - e. Never (1)
8. [If Q5 = “No”] How often (approximately) do you currently play video games?
- a. Daily (10)
 - b. Weekly (8)
 - c. Monthly (6)
 - d. Few times a year (4)
 - e. Never (2)
9. How good do you feel you are at playing video games?
- a. Very good (4)
 - b. Moderately good (3)
 - c. Not very skilled (2)
 - d. No skill (1)
10. Approximately how many hours per week do you spend playing video games that involve learning the layout of virtual environments (e.g., Halo, Call of Duty, World of Warcraft)?
- a. 0 (1)
 - b. 1-5 (2)
 - c. 6-10 (3)
 - d. 11-15 (4)
 - e. 16-20 (5)
 - f. 20+ (6)
11. If you do not currently play video games that involve learning the layout of environments, did you play these games in the past?
- a. Yes (1)
 - b. No (0)
 - c. N/A (0)
12. [If Q11 = “Yes”] How many hours per week?
- a. 0 (1)
 - b. 1-5 (2)
 - c. 6-10 (3)
 - d. 11-15 (4)
 - e. 16-20 (5)

f. 20+ (6)

13. How many years have you/did you consistently play video games (lifetime)? [*Open-ended response*]

Appendix B

Figure B1. Individual progesterone concentrations in their early follicular (menses) and ovulatory window phases.



Appendix C

Chapter IV. Other Tasks Measured in the Context of a Larger Study

Additional tasks measured, but not assessed in this study, include: the Selective Reminding Task (Buschke, 1973; Hannay & Levin, 1984), the Digit Span subtest from the Wechsler Intelligence Scale for Children: Fourth Edition (Wechsler, 2009), the Digit Symbol Substitution Test (Smith, 1973), the Stroop Test (Stroop, 1935), Fluencies tasks (Delis, Kaplan, & Kramer, 2000), the NIH Cognitive Toolbox Battery (picture vocabulary, oral reading recognition, list sorting working memory, pattern comparison processing speed, picture sequence memory, flanker inhibitory control and attention, dimensional change card sort, RAVL, and the oral symbol digit), and the verbal N-back task (as used in Jacobs & D'Esposito, 2011).

Questionnaires administered, but not assessed are: the RAN 36-item Health Survey (Sherbourne & Stewart, 1991), Migraine Screening Questionnaire (Láinez et al., 2010), International Physical Activity (Craig et al., 2003), State Trait Anxiety Inventory (Spielberger, 1989), Life Satisfaction (Eaton et al., 2004), Menopause-Specific Quality of Life Questionnaire (Hilditch et al., 1996), Adverse Childhood Experience Questionnaire (Felitti et al., 1998), PTSD Checklist – Civilian Version (Lang & Stein, 2005), Measurement of Everyday Cognition (Tomaszewski Farias et al., 2011), Edinburgh Handedness Inventory (Veale, 2014), Pittsburgh Sleep Quality Index (Buysse et al., 1989), Biberoglu & Berman Scale for measuring endometriosis pain (Rush et al., 2019), and a Medication Adherence Questionnaire (De las Cuevas & Peñate, 2015). Structural and functional magnetic resonance imaging (MRI) was additionally included. Scans included whole brain anatomy, hippocampus segmentation, white matter using Diffusion Spectrum Imaging, and cerebral blood perfusion via Arterial Spin Labeling. Finally, blood draws additionally included

follicle-stimulating hormone, luteinizing hormone, sex hormone binding globulin, dehydroepiandrosterone sulfate, and DNA to assess genetic data as a marker of Alzheimer's disease risk.