Sex differences in spatial navigation during early aging and AD

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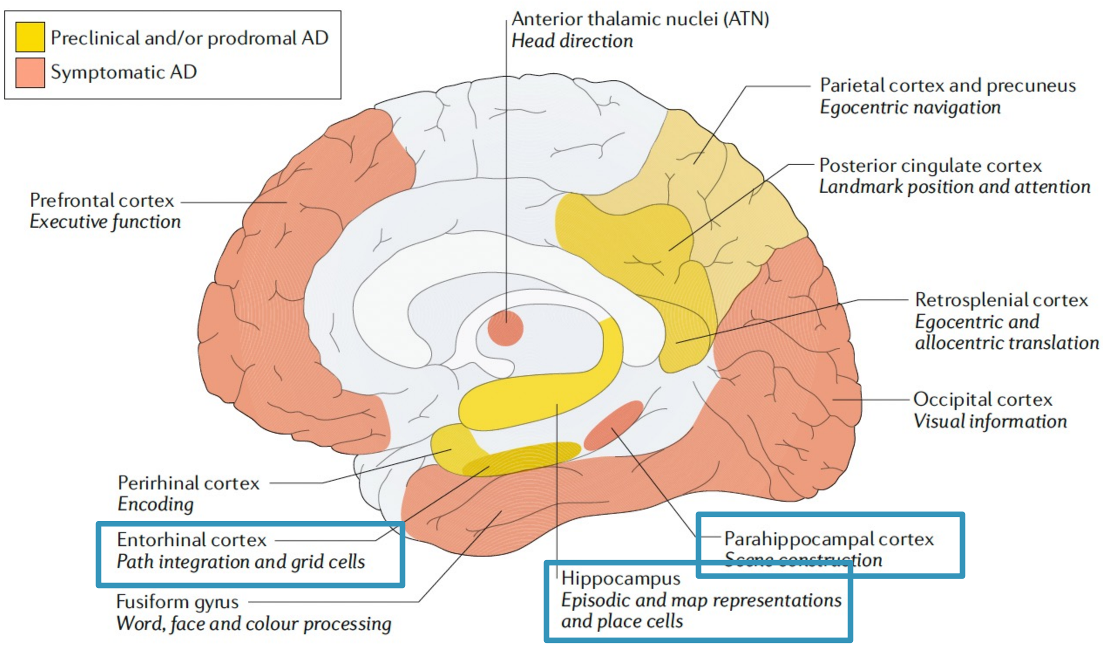
Finding Your Way

- How does the brain learn spatial information?
- How do individuals differ in their navigational abilities?
- Synthesis of cognitive and neuroscience approaches
  - Immersive virtual reality, GPS tracking, fMRI, EEG

Alzheimer's Disease and Navigation

- Large overlap between brain regions affected earliest by AD and those that are important for navigation

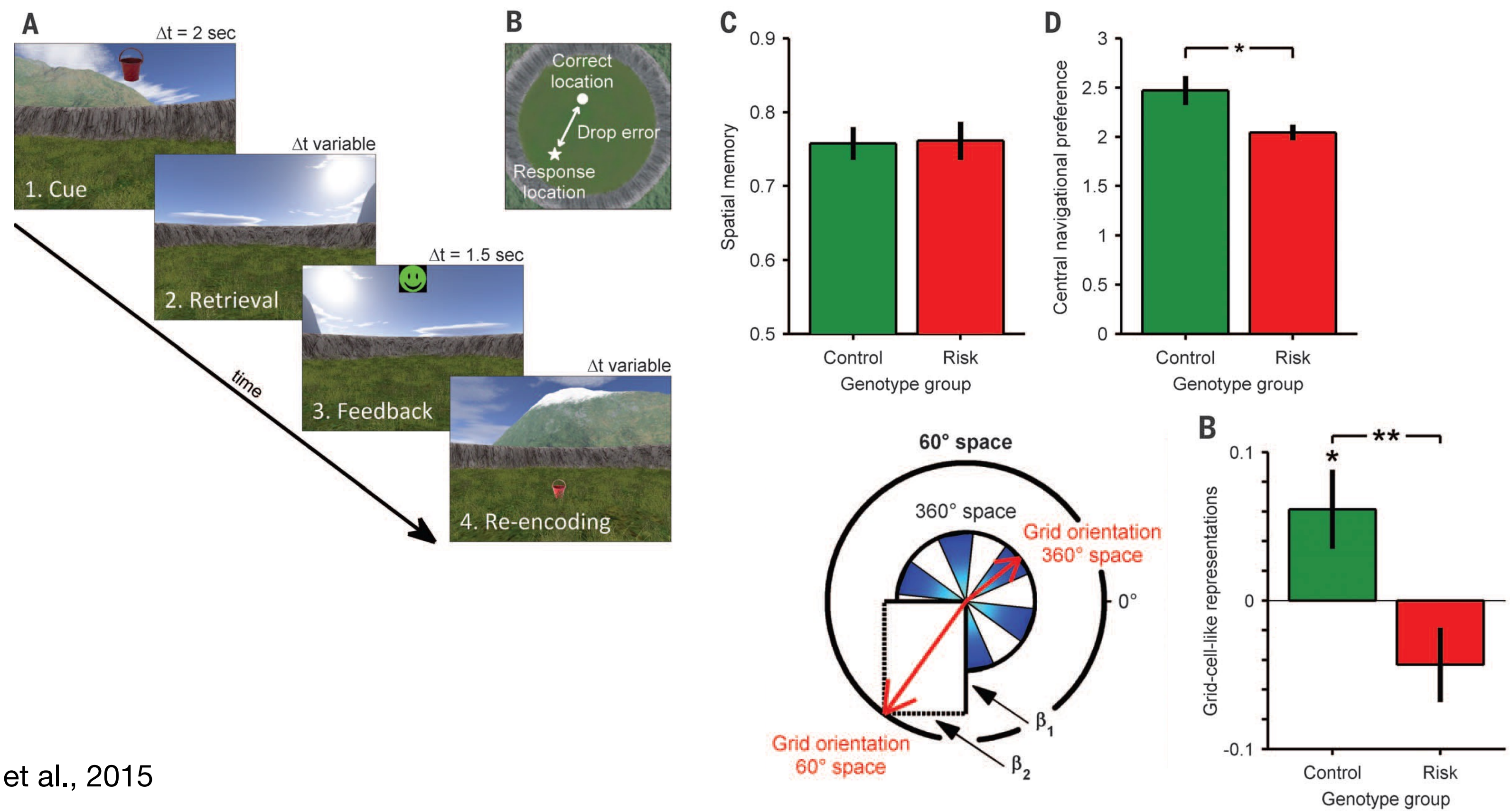


White matter tracts:
Fornix
Cingulum Bundle

Coughlin et al., 2018

Alzheimer's Disease and Navigation

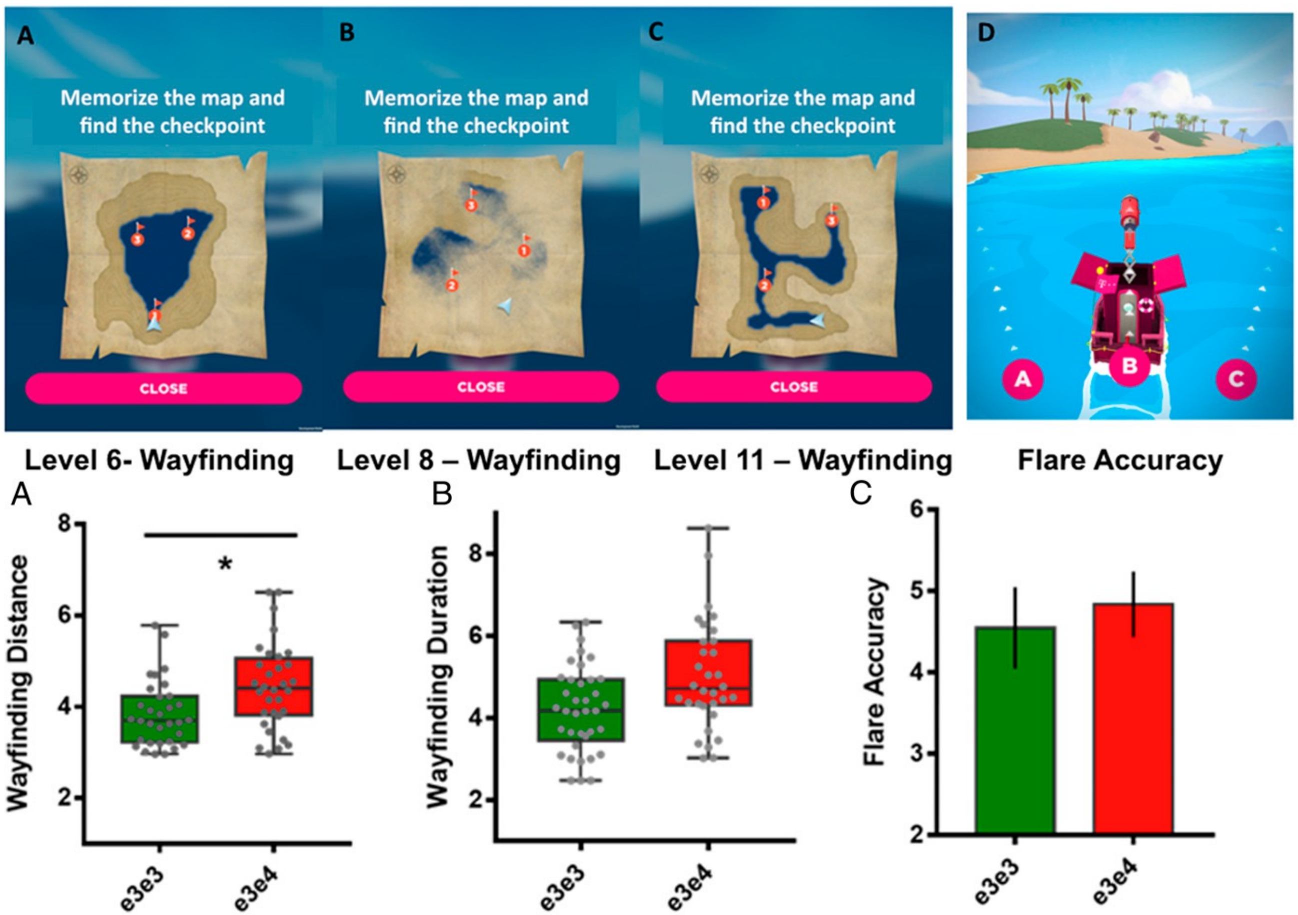
- Changes in navigation behavior and function in entorhinal cortex grid cells for those at genetic risk decades before disease symptoms



Kunz et al., 2015

Alzheimer's Disease and Navigation

- Changes in navigation behavior for those at genetic risk using a mobile phone game



Coughlin et al., 2019

Alzheimer's Disease and Navigation

- Navigation has emerged as an early marker for detecting people at risk for dementia (Kunz et al., 2015; Stangl et al., 2018; Coughlin et al., 2019)
- Women have twice the risk for dementia than men
- Sex differences in navigation have been frequently observed
- Sex hormones influence organization of the hippocampus (Frick et al., 2018; Yagi & Galea, 2019)

Questions

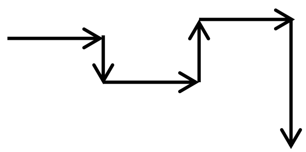
- Can we use navigation as a tool to determine risk for dementia, especially for women?
- How do sex differences in navigation change during the course of aging?
- Do any changes in navigation ability relate to the menopausal transition?
- Can we identify aspects of navigation that provide even earlier markers for AD risk?
- What aspects of an individual's navigation ability track with their long-term risk for AD?

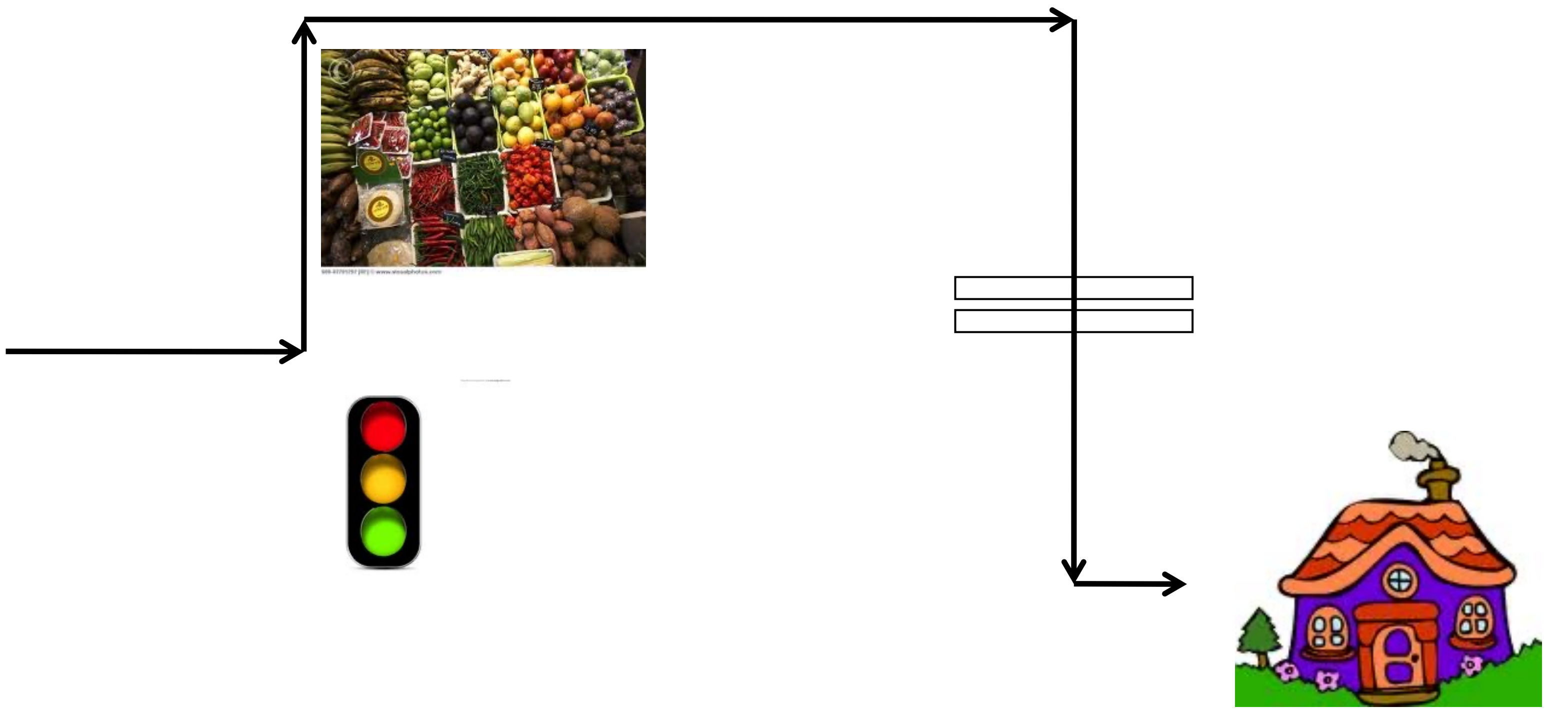
Types of Spatial Knowledge

- Landmark
  - Salient objects or locations that provide navigational cues

Types of Spatial Knowledge

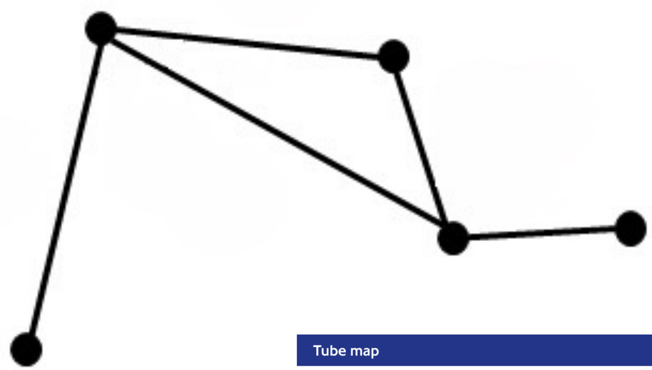
- Route
  - Series of place-action associations

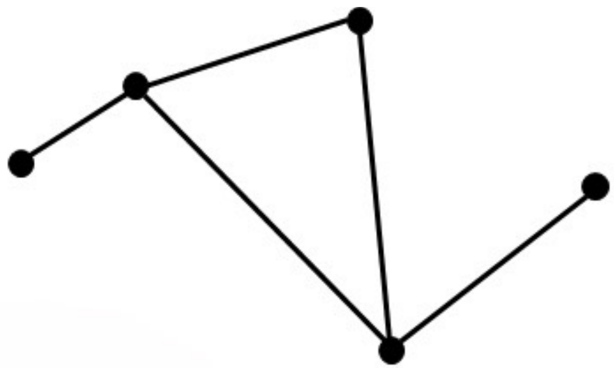




Types of Spatial Knowledge

- Graph
  - A network of place nodes linked by path edges

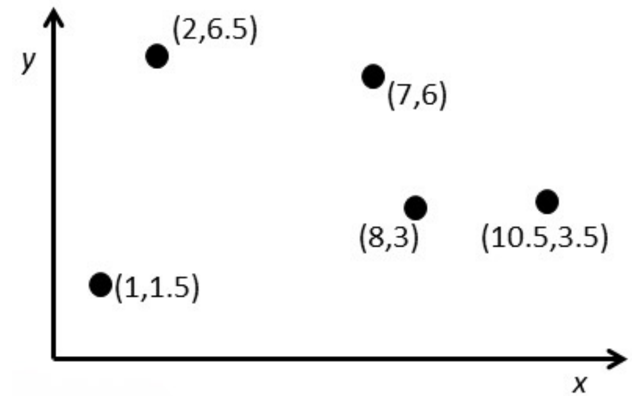


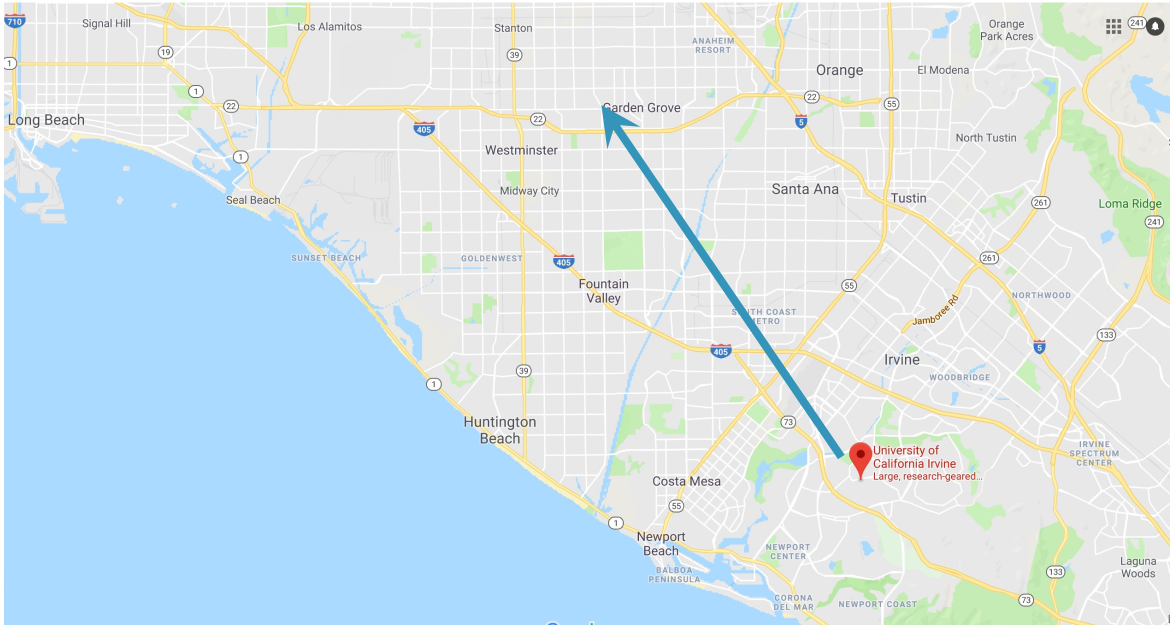


Chrastil & Warren, *PLOS ONE*, 2014

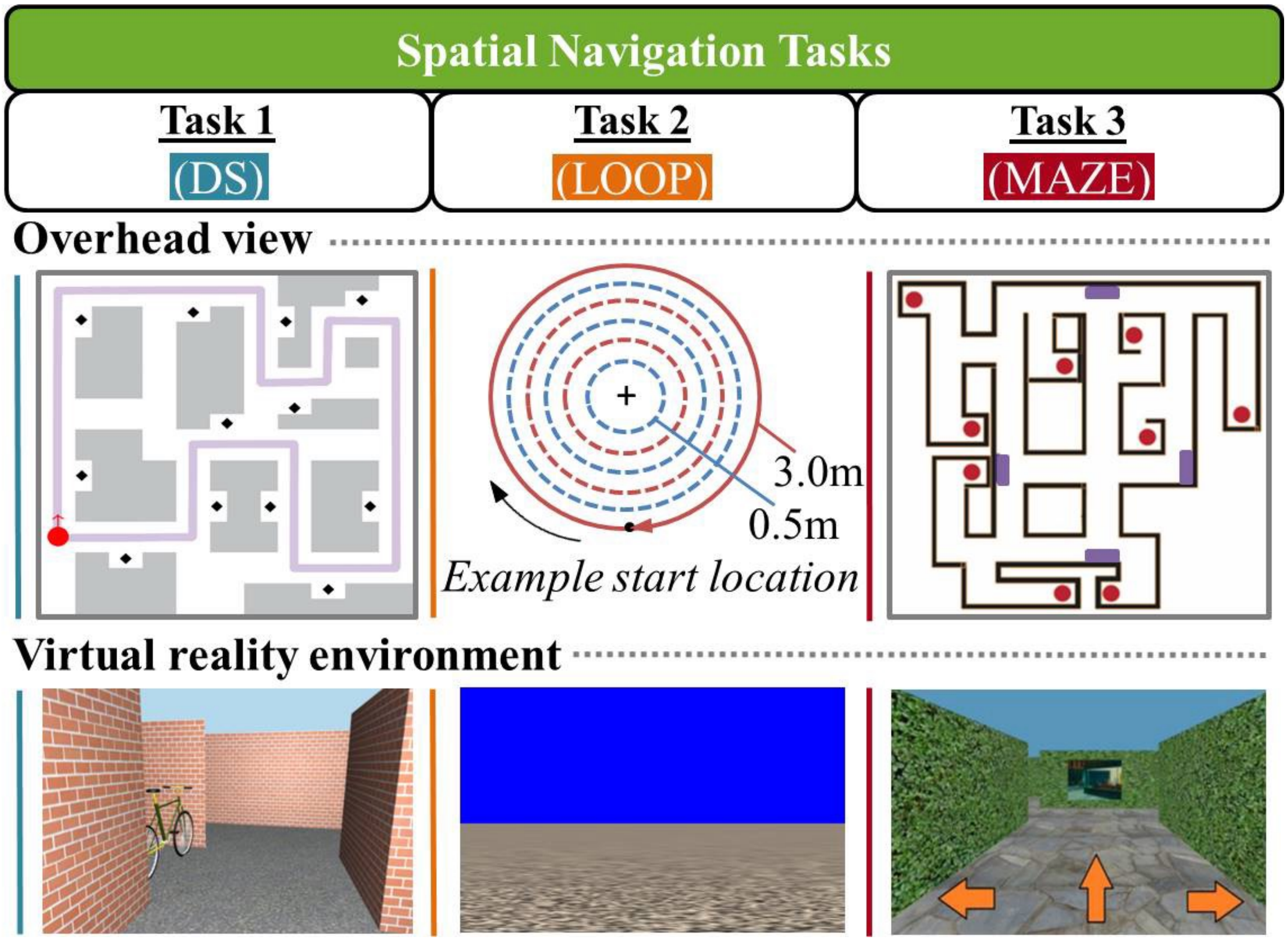
Types of Spatial Knowledge

- Survey
  - Maplike knowledge metric distances and angles between locations
  - Enables shortcuts





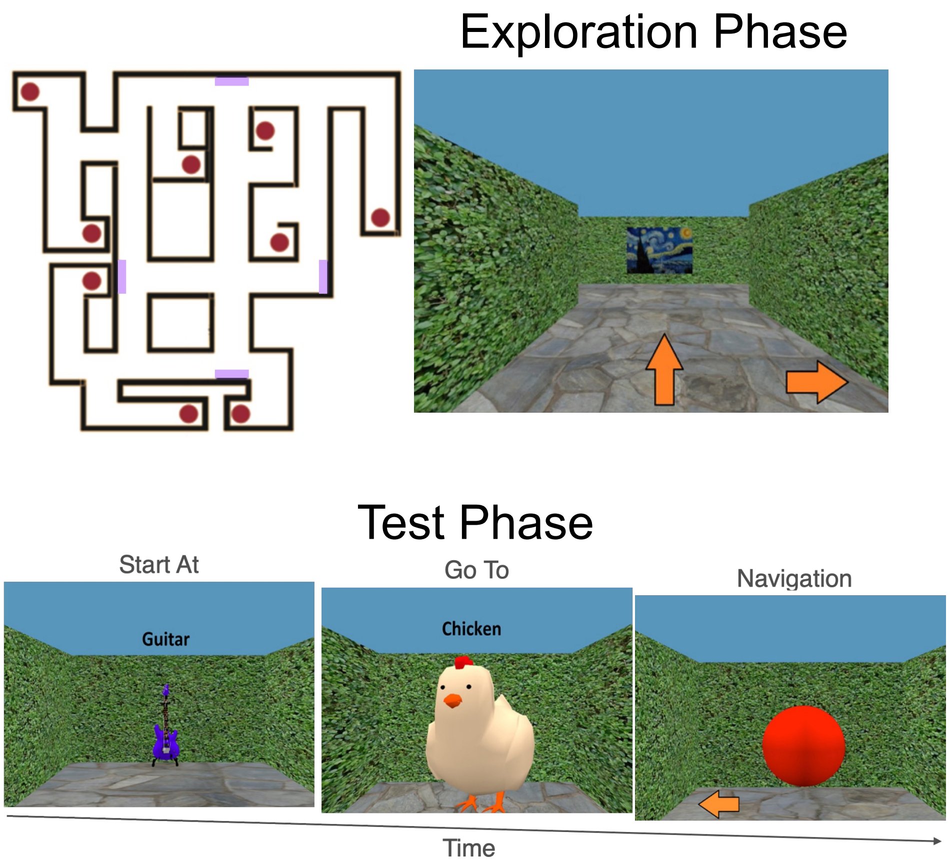
Early Aging

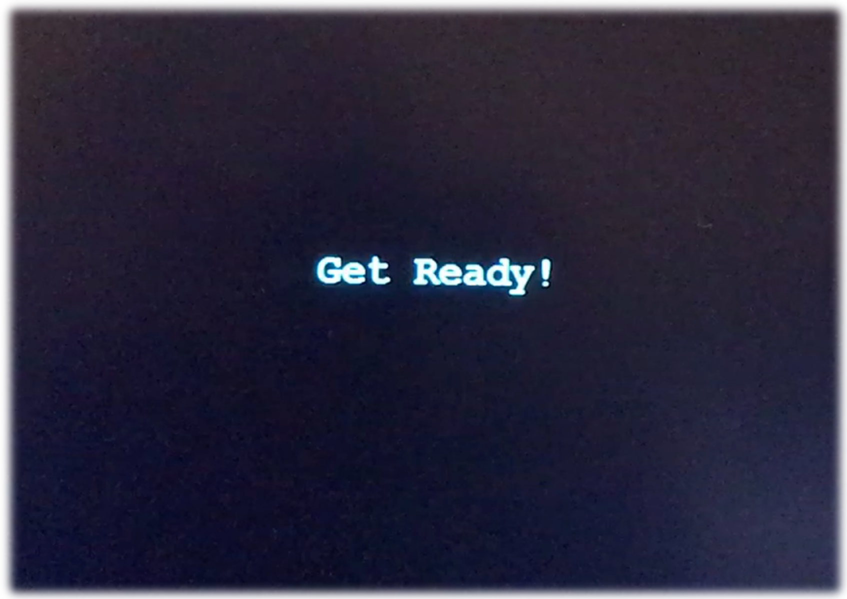


- Midlife women and men (ages 45-55)
- Younger adults (ages 18-35)
- Pre-, peri-, and post-menopausal women
- Chronological aging and reproductive aging
- With Drs. Emily Jacobs and Mary Hegarty at UCSB

Yu et al., *Psych Science,* 2021

Maze Learning – Graph Knowledge

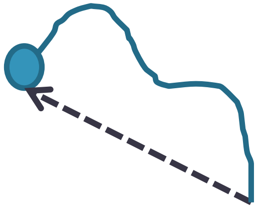




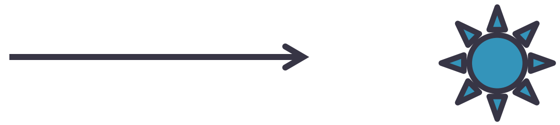
Path Integration

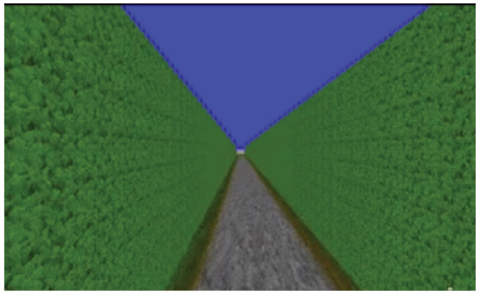
- Continuous updating of position and orientation during movement in an environment
- Might underlie survey knowledge
- Relies on entorhinal cortex, hippocampus, and other MTL regions
- Previous studies found path integration deficits in aging populations, although mixed on AD

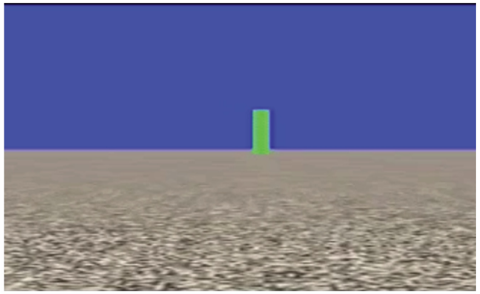
- Tracking a location



- Tracking translation and rotation



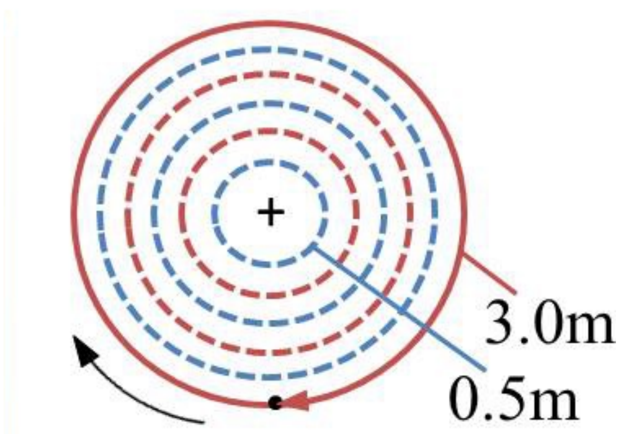


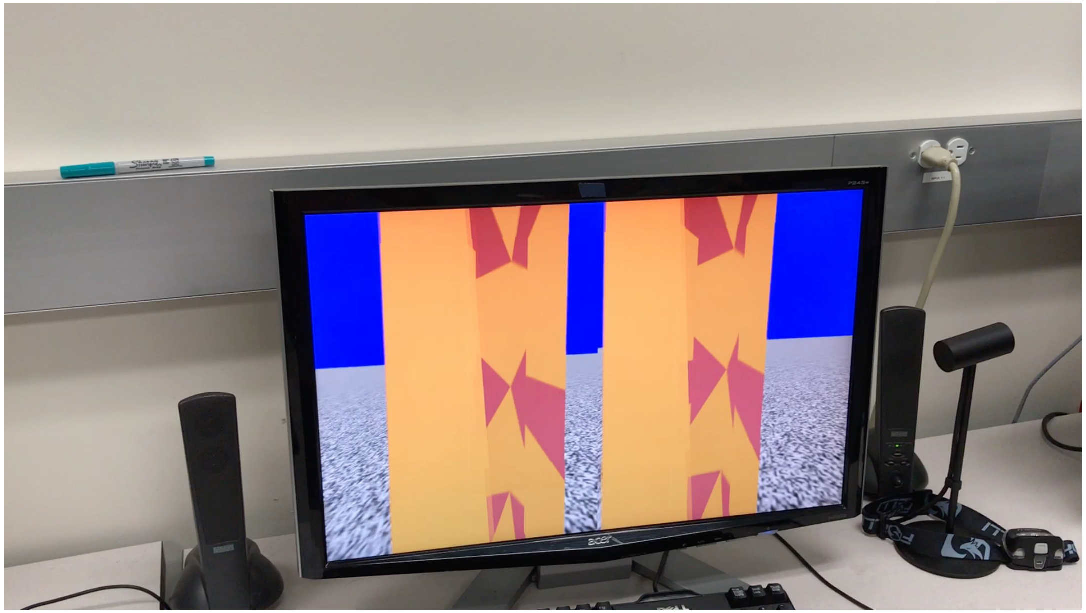


Chrastil & Warren, *Experimental Brain Research*, 2017
Chrastil & Warren, *JEP:HPP, 2021*

Path Integration – Loop Closure

- Walk people in a circular path
- Click when they think they return to the start

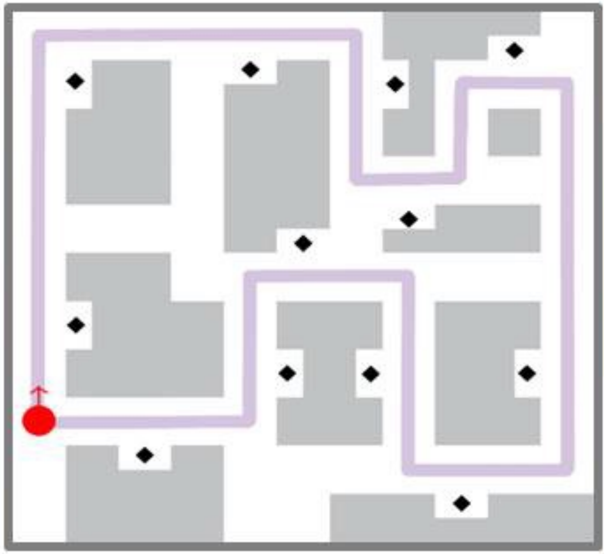




Chrastil et al., *Cognition,* 2019

Strategies – Dual Solution Paradigm

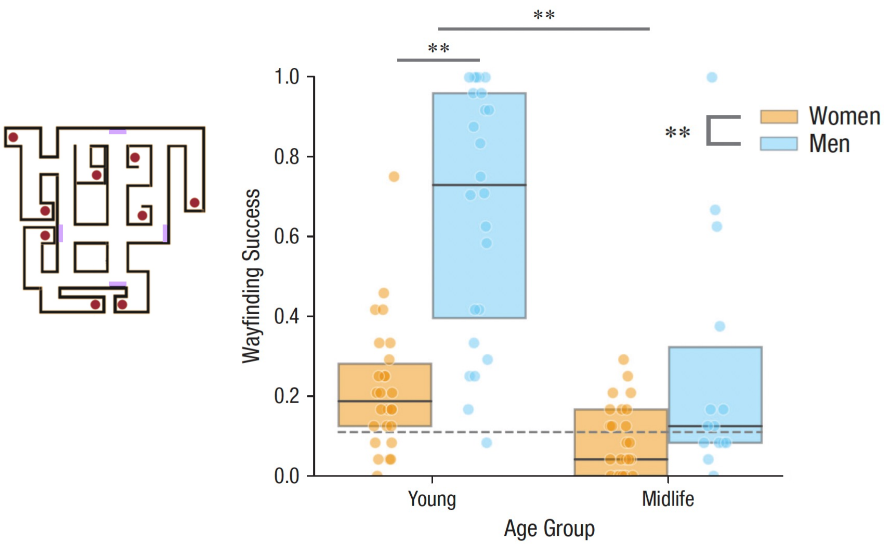
- Follow route 5 times in virtual maze
- Then go from one object to another object (objects visible)
- Do people follow the route they know or take a shortcut?



Abilities Differ by Sex and Age

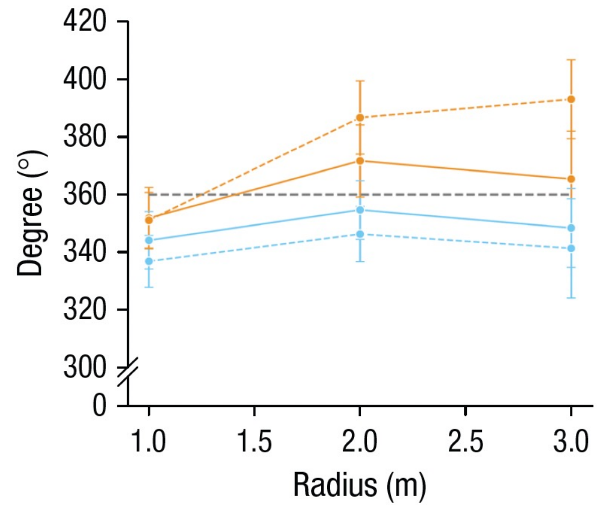
Shuying Yu

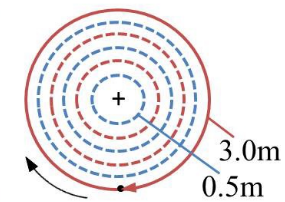
Maze Task



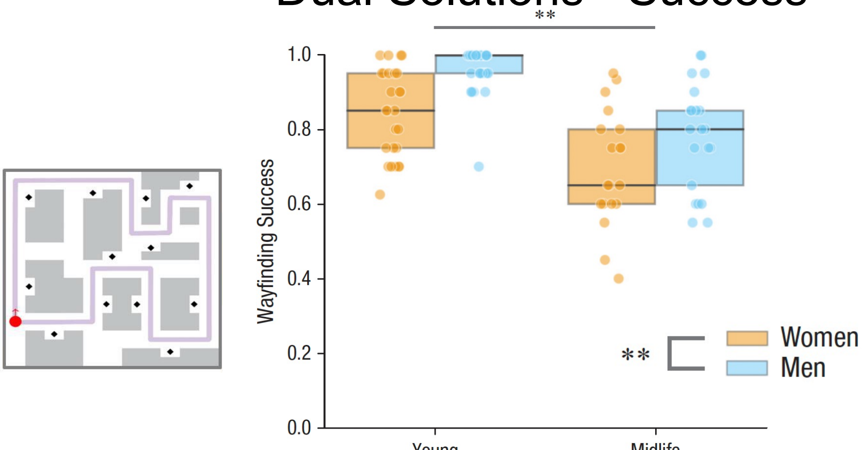
Loop Task

Degrees Traveled

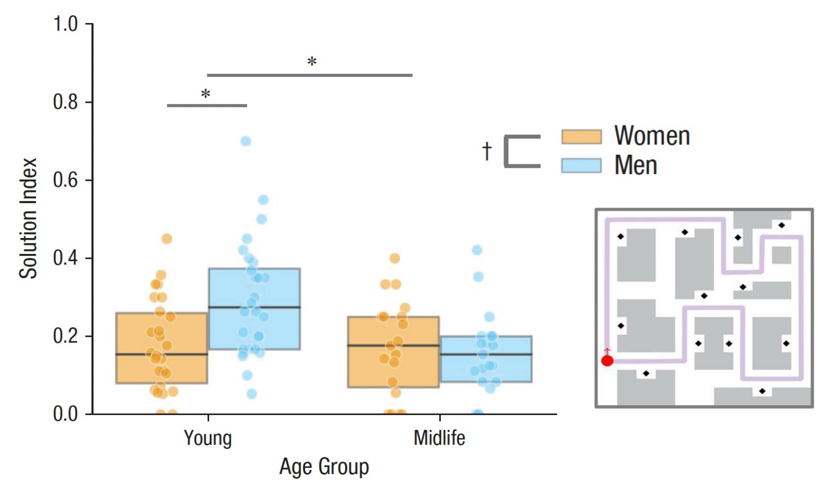




Dual Solutions - Success

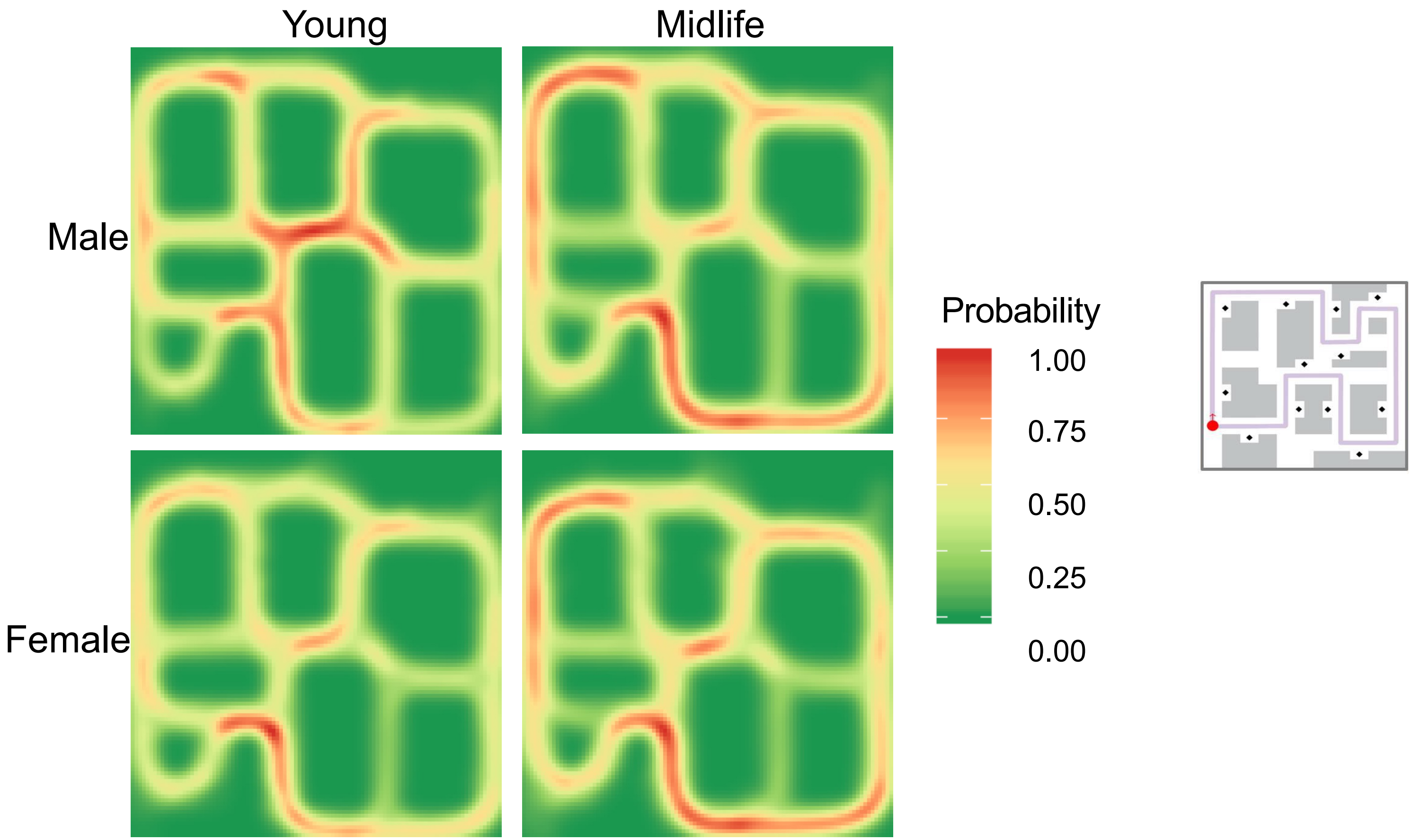


Dual Solutions - Shortcuts



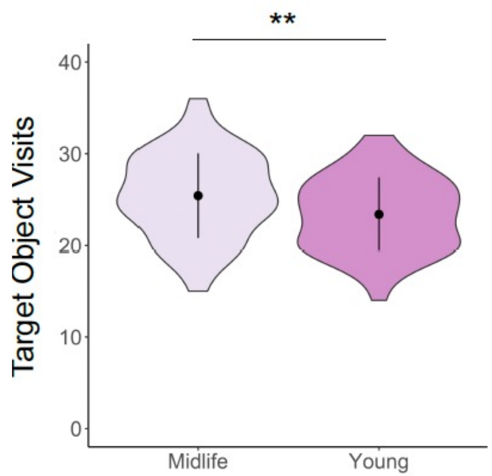
Yu et al., *Psych Science*, 2021

Heatmaps of Test Trials

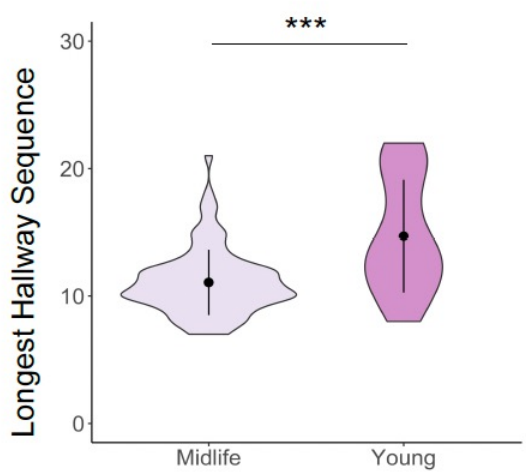


Exploration Behavior Changes with Age

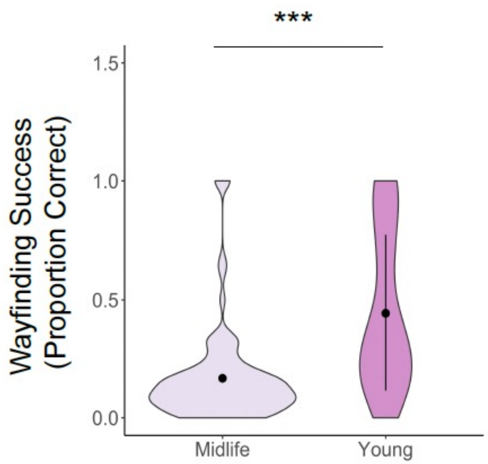
- Midlife adults (ages 45-55) had more object visits than young, less time in hallways, and performed worse overall

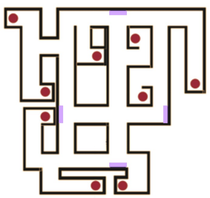


Midlife > Young
($p = 0.007$; $d = 0.46$)



Midlife < Young
($p < 0.001$; $d = 1.08$)





Midlife < Young
($p < 0.001$; $d = 1.08$)

Vaisakh Puthusseryppady

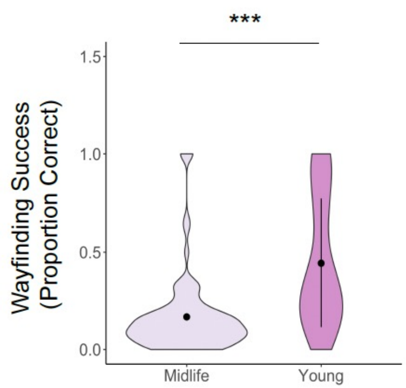
n=51 younger
n=112 midlife

Puthusseryppady et al., *under review*

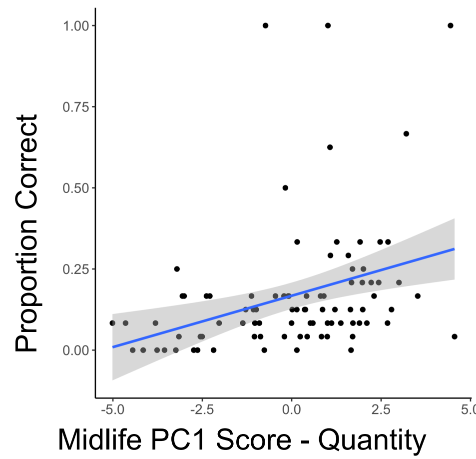
Exploration Behavior Changes with Age

- Exploration quantity and quality were correlated with performance in midlife adults

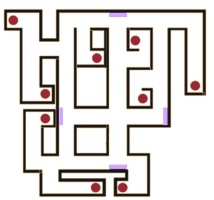
n=51 younger
n=112 midlife

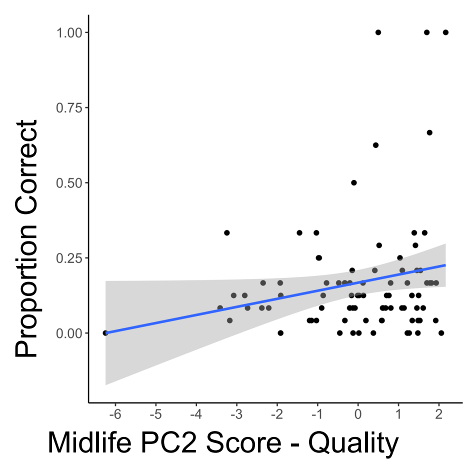


Midlife < Young
($p < 0.001$; $d = 1.08$)



$r = 0.34$
$p < 0.001$



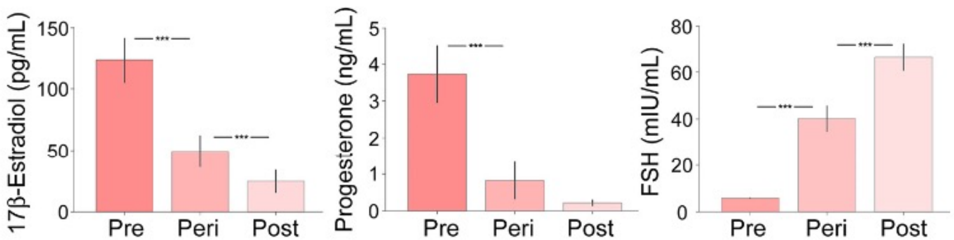


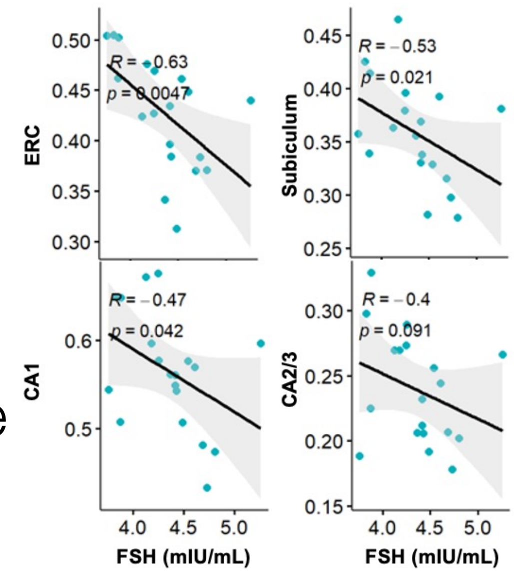
$r = 0.21$
$p = 0.038$

Vaisakh Puthusseryppady

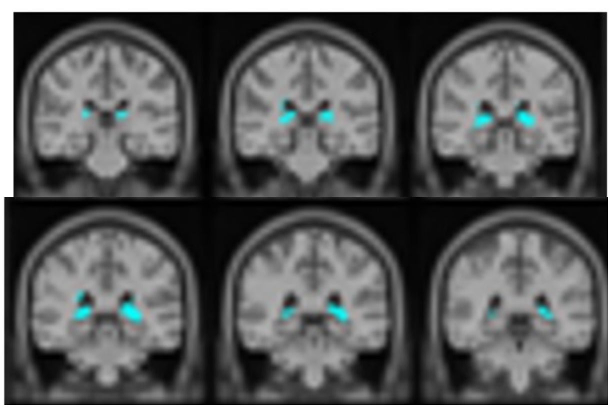
Puthusseryppady et al., *under review*

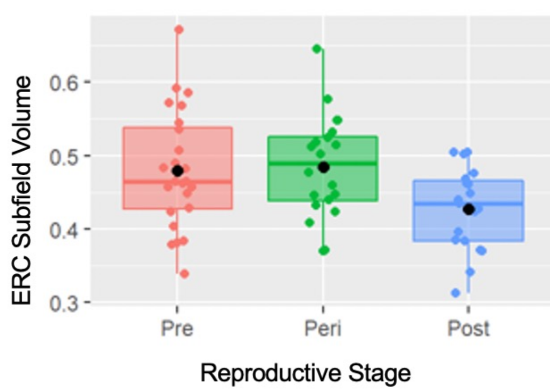
Preliminary Neuro/Menopause Findings

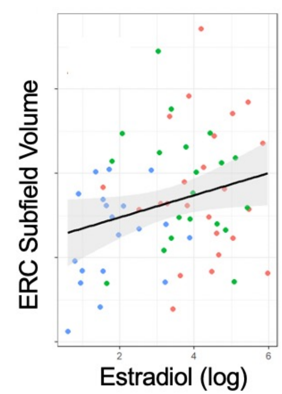




- Greater progesterone levels in midlife are related to increased white matter integrity in limbic regions
- Reproductive stage impacts entorhinal cortex volume
- FSH post-menopause associated with reduced volumes in medial temporal subregions

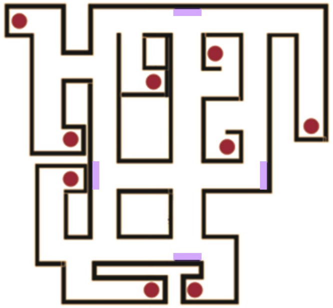






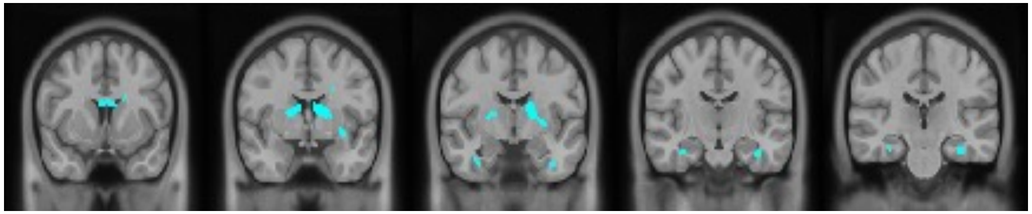
Preliminary Neuro/Menopause Findings

- Differing directions of associations between performance and white matter integrity in males and females
- Females overall show positive relationship between performance and white matter integrity in fornix, cingulum bundle, cerebellum (n=57)
- Males have negative correlations in fornix (n=16)

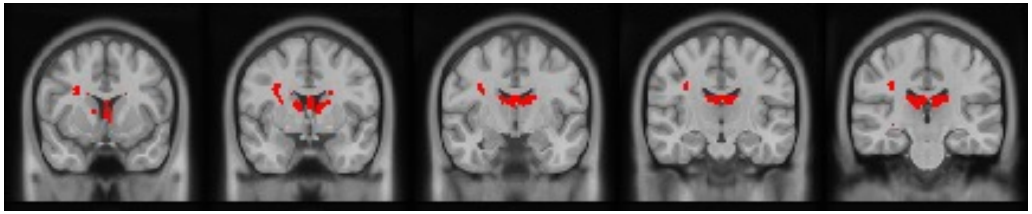


Maze

Females



Males

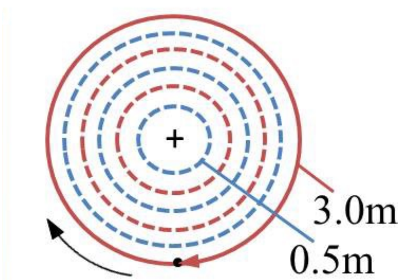


Daniela Cossio

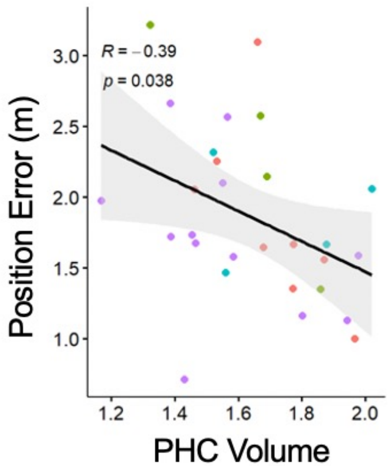
Preliminary Neuro/Menopause Findings

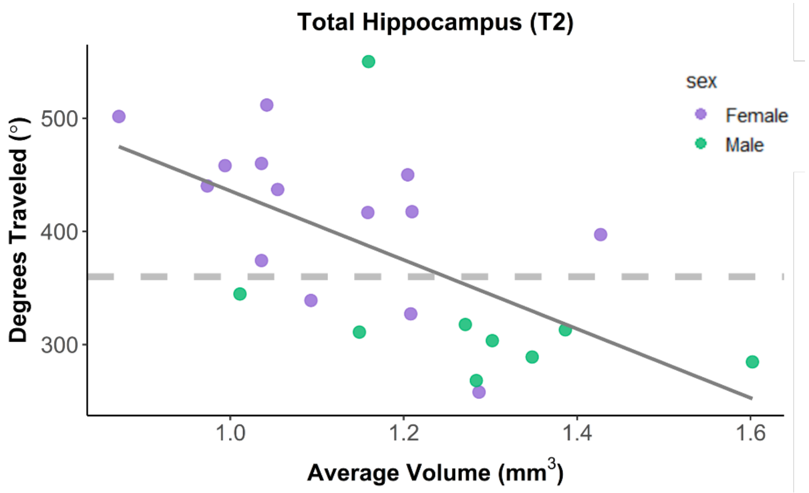
- Reduced parahippocampal volume in midlife is associated with greater position error in loop task (n=26)
- Total hippocampal volume in midlife is associated with degrees traveled in the loop task
- White matter integrity in fornix related to accuracy in pre-menopausal women but not in peri- or post-menopausal women

Daniela Cossio



Loop

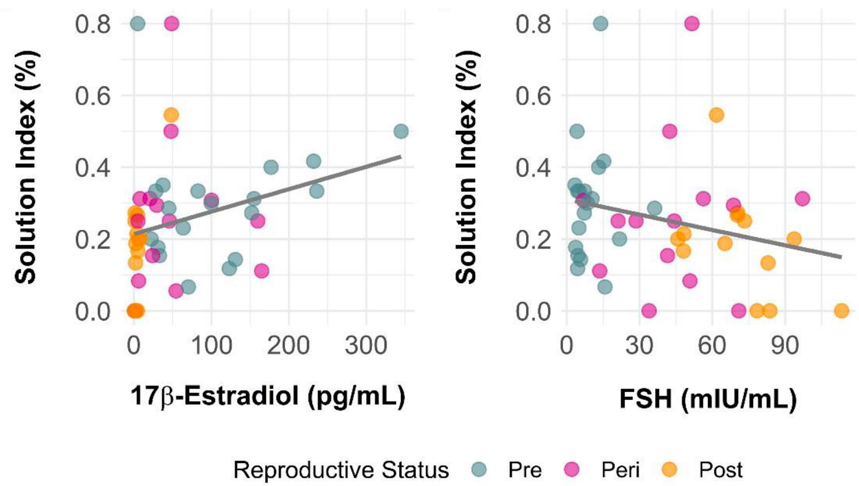


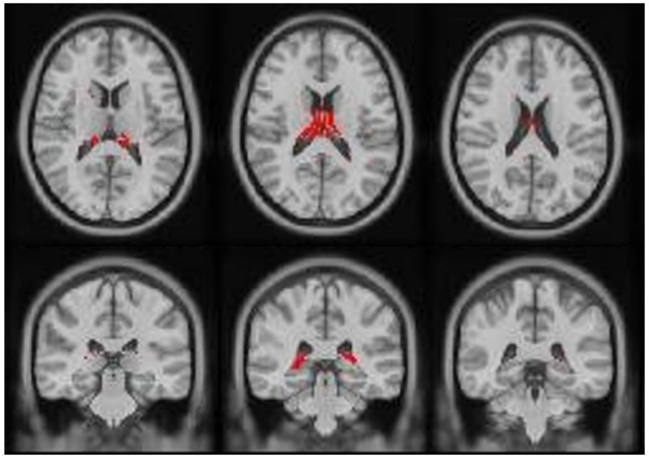


Shuying Yu

Preliminary Neuro/Menopause Findings

- Rising FSH and decreasing estradiol are associated with increased reliance on habitual routes in midlife women (n=74)
- Larger gray matter volume in CA2/3 associated with taking more shortcuts in peri-menopausal women (n=18)
- White matter integrity in fornix is associated with taking more novel shortcuts in midlife adults (n=77)





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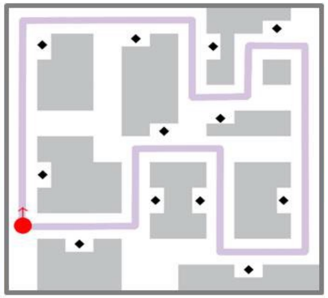
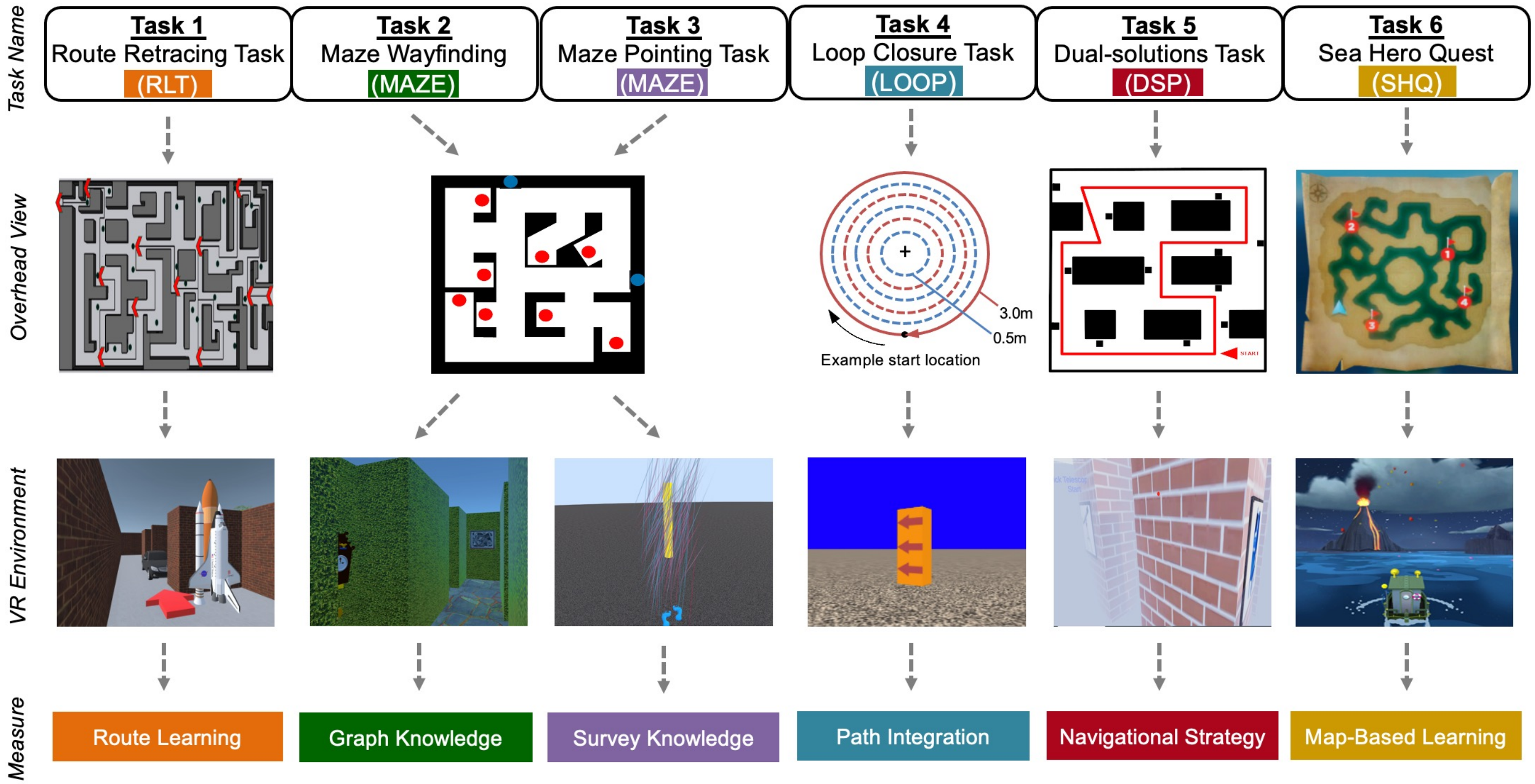


Strategy

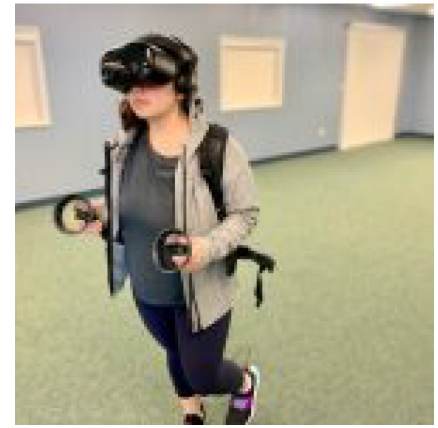
Shuying Yu

Next Steps – Aging

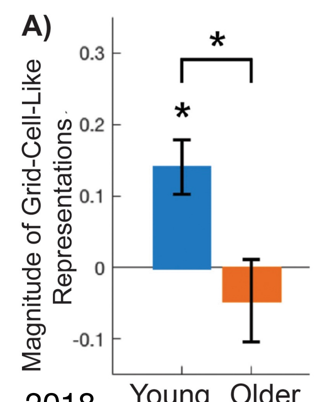
- More complete spatial battery, including immersive VR



Next Steps – Menopause



- More complete spatial battery, including immersive VR
  - Reduced motion sickness
  - Provides proprioception and vestibular cues
- Hormone assay, AD risk factors
- Imaging session of structure and resting state function
- Including scan to measure grid cell-like brain activation



Stangl et al., 2018

Next Steps – Alzheimer's

- Alzheimer's Disease and exploration behavior
- Individual differences and AD – longitudinal study
- Which aspects of spatial navigation are most relevant for AD risk?

Vaisakh Puthusseryppady

Questions

- Can we use navigation as a tool to determine risk for dementia, especially for women?
- How do sex differences in navigation change during the course of aging?
  - Some are reduced, some have no sex difference (path integration)
- Do any changes in navigation ability relate to the menopausal transition?
  - Relationships with hormone levels, menopausal staging
- Can we identify aspects of navigation that provide even earlier markers for AD risk?
  - In progress
- What aspects of an individual's navigation ability track with their long-term risk for AD?
  - Future work

Thank you!

UCI
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CNSI California NanoSystems Institute
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