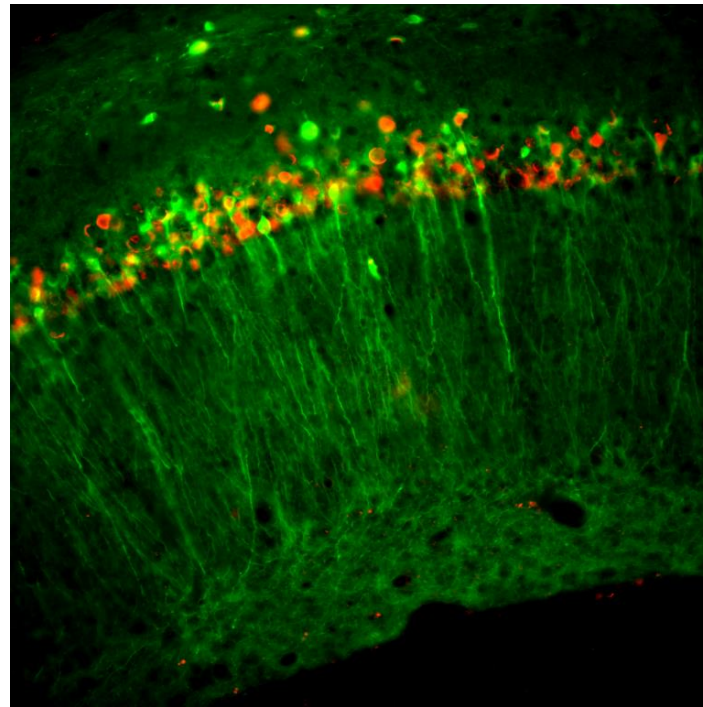


*Opening the Therapeutic Window
for Estrogen Treatment through
Hippocampal ER-alpha Overexpression*



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April 29, 2015

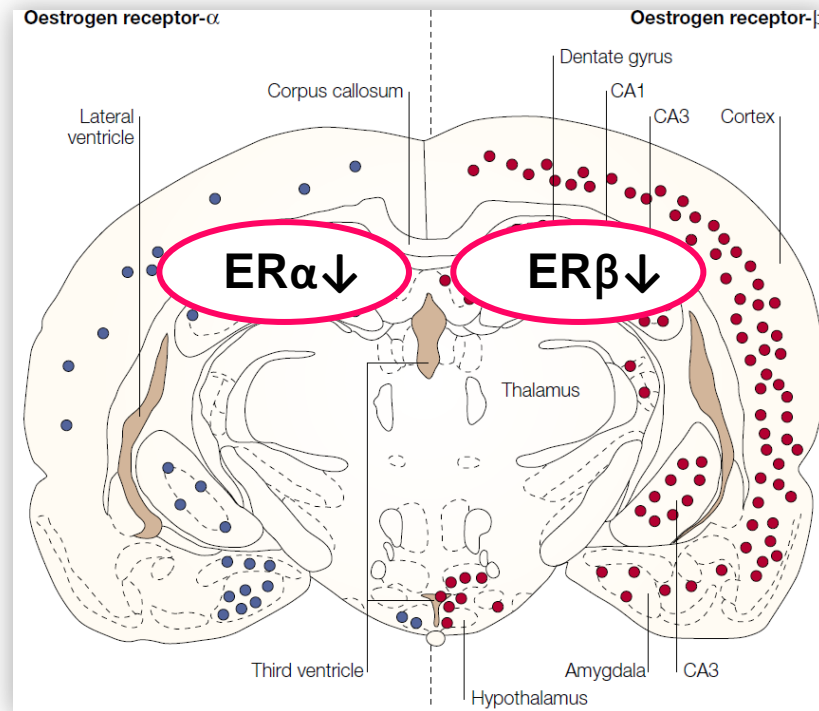
Therapeutic Window

- Average age for the onset of menopause is 51 year of age
- Estrogen therapy promotes cognitive function if treatment is initiated around the time of onset
- Treatments initiated at ages 65 and over have no effect

What is regulating this therapeutic window?

Estrogen Receptors

- Estrogen receptors: alpha ($ER\alpha$) and beta ($ER\beta$)
- Estrogen receptor levels decline with age in the hippocampus



(Shughrue 1997, Mehra, 2005)

Experimental Design

Fischer 344 female rats

* AAV1 for ER α , ER β or GFP

^ Estrogen benzoate (EB) or oil treatment

GFP+EB, n=13

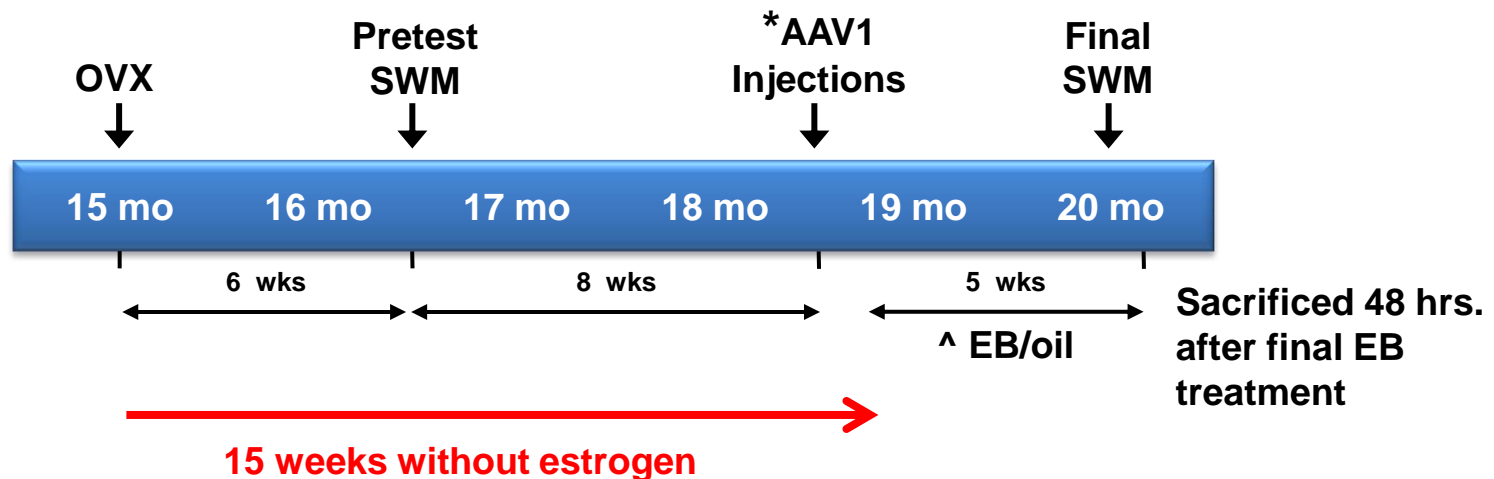
ER β +EB, n=11

ER α +EB, n=13

GFP+Oil, n=12

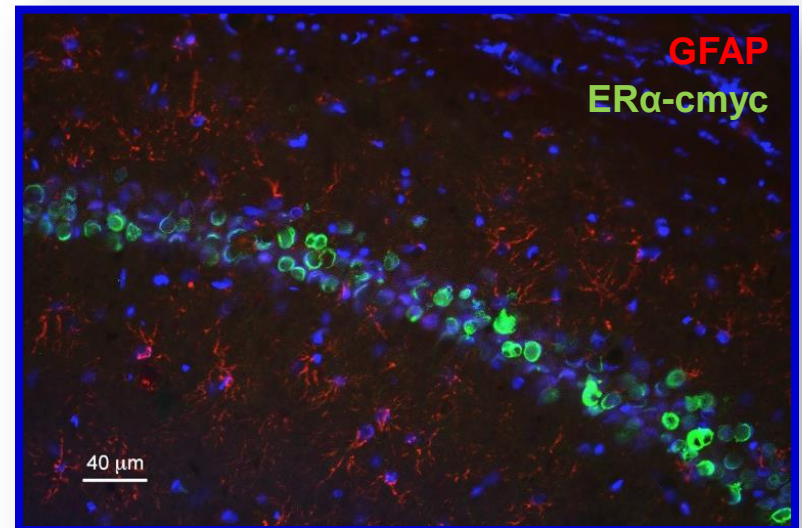
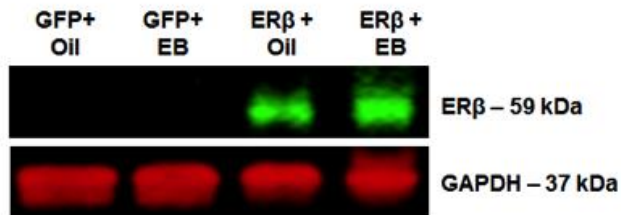
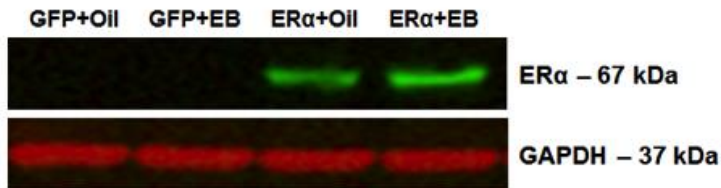
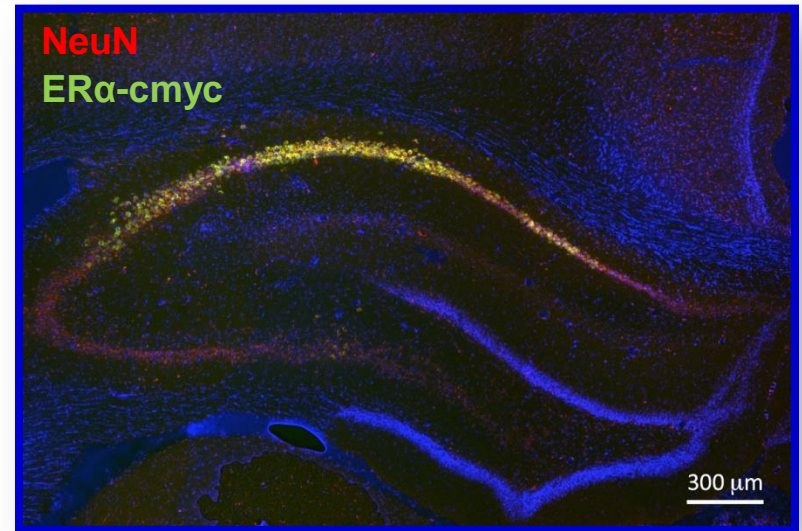
ER β +Oil, n=11

ER α +Oil, n=12

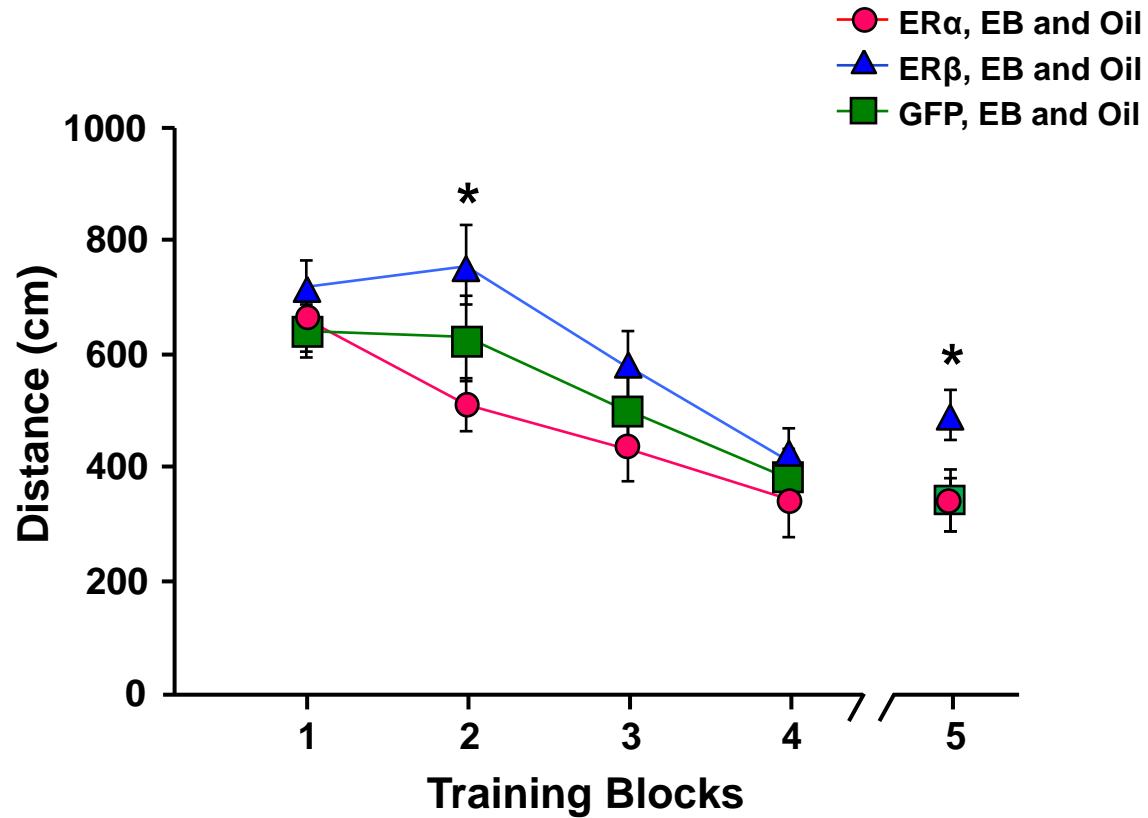


Efficacy of AAV1

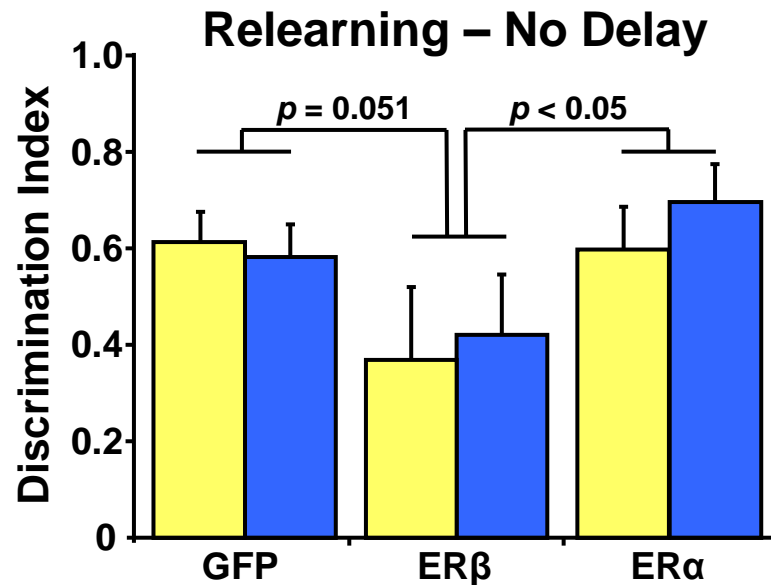
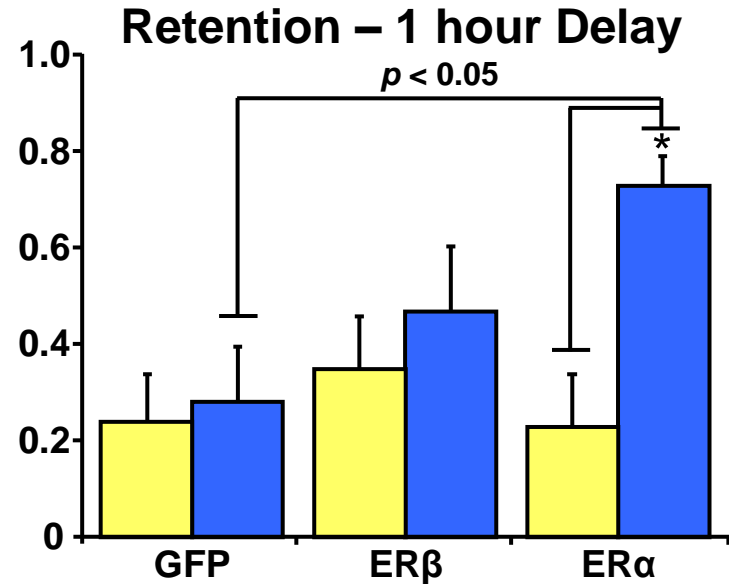
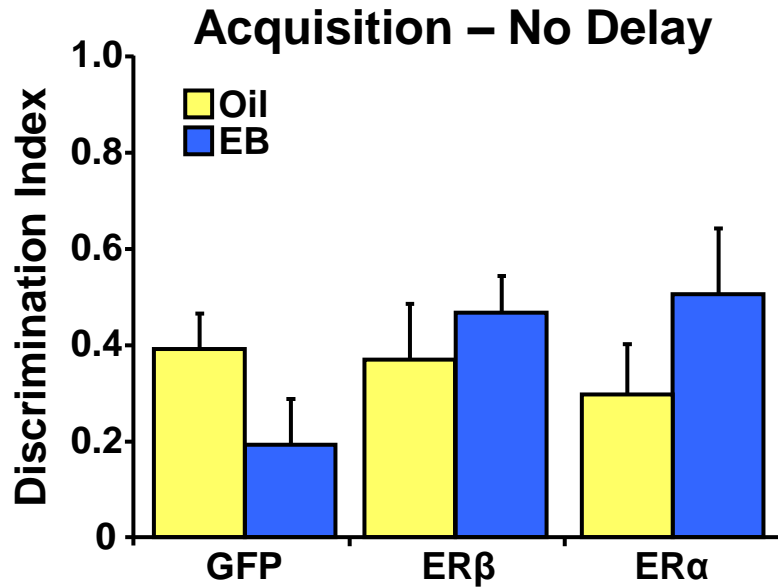
- CA1 region of hippocampus
- ~2800 μm anterior/posterior
- Expression in NeuN+ neurons



Spatial Training

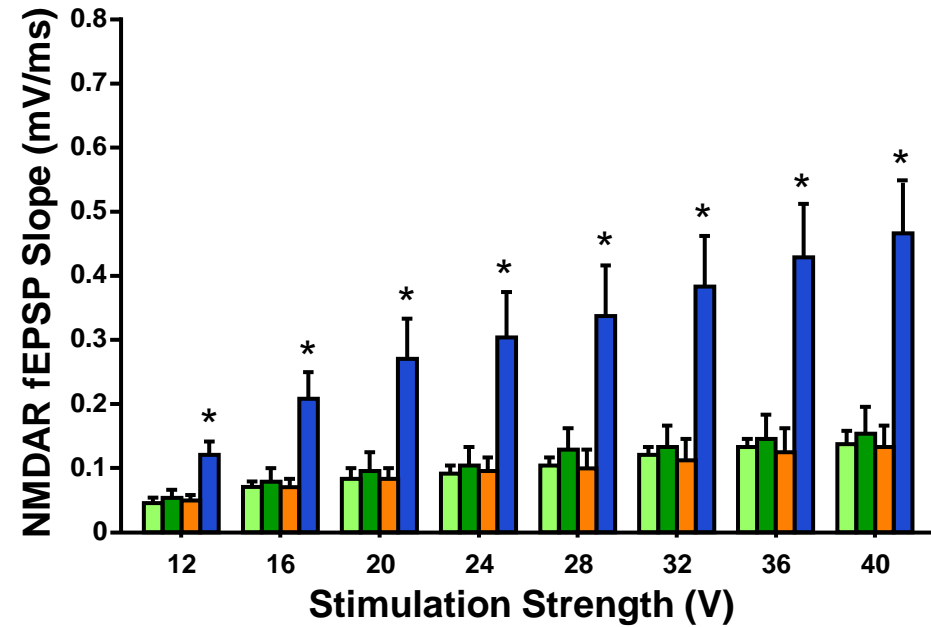
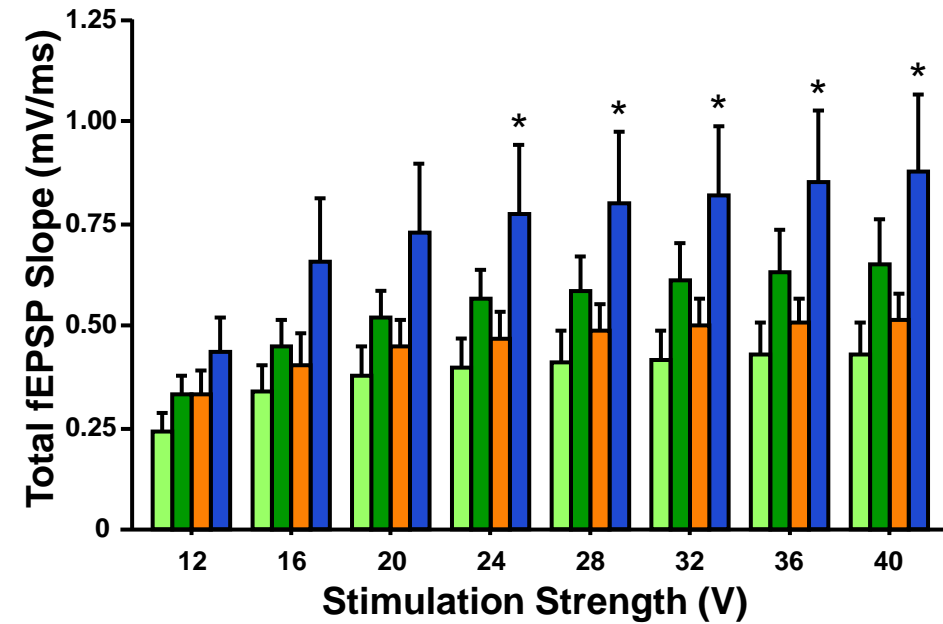


Spatial Water Maze – Probe Trials



Synaptic Response

- GFP+Oil, n=4/8 animals/slices
- GFP+EB, n=n=4/8 animals/slices
- ER α +Oil, n=4/8 animals/slices
- ER α +EB, n=5/10 animals/slices



Conclusion

- Timeframe of experiment is outside of the therapeutic window (EB treatment had no effect on GFP control animals)
- Increasing expression of ER α
 - restored the beneficial effects of E2 therapy on hippocampal-dependent spatial memory
 - increased the NMDAR-mediated synaptic responses
- Use this information to design healthier pharmacological choices for aging women

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