



# Estrogen Influences on Cognitive Aging in the Monkey

Peter R. Rapp  
Department of Neuroscience  
Mount Sinai School of Medicine  
New York, NY

# Background

- Estrogen prominently influences the structure and function of multiple neural systems implicated in normal cognition, including the hippocampus
- Experimental and naturally occurring ovarian hormone fluctuations can have a variety of cognitive effects
- Proposal: Ovarian hormone decline associated with menopause might regulate the course of cognitive aging

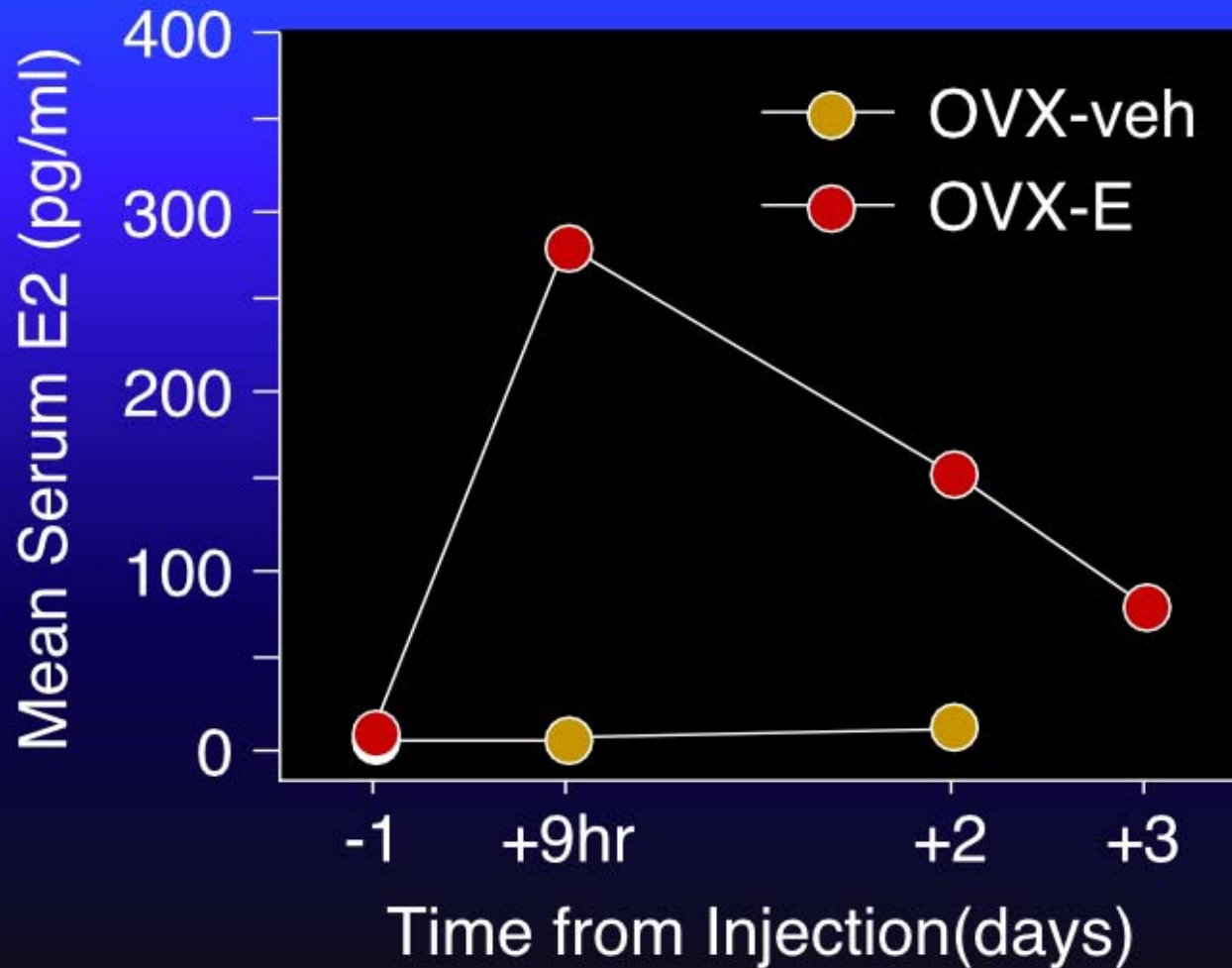
*“As estrogens have been found in animal models to be associated with the maintenance and protection of brain structures, it is biologically plausible that maintaining high levels of estrogens in postmenopausal women by medication could be protective against cognitive decline.”*

Hogervorst et al., 2002

# Experimental Design:

- 16 pre-/perimenopausal aged monkeys, mean age ~22 years
- Ovariectomy prior to neuropsychological testing
- Random assignment to vehicle (OVX-veh, n=8) or estrogen treatment (OVX-E, n=8) groups
- Estradiol cypionate, 100 $\mu$ g/1ml peanut oil, IM, every 21d
- Cognitive assessment: DR, DNMS and OD
- Neurobiological assessment

# Treatment Time-course: Serum Estradiol



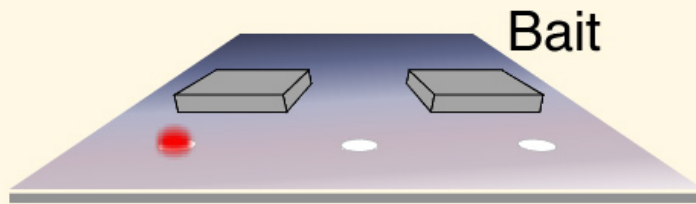
# Experimental Design:

- 16 pre-/perimenopausal aged monkeys, mean age ~22 years
- Ovariectomy prior to neuropsychological testing
- Random assignment to vehicle (OVX-veh, n=8) or estrogen treatment (OVX-E, n=8) groups
- Estradiol cypionate, 100 $\mu$ g/1ml peanut oil, IM, every 21d
- Cognitive assessment: DR, DNMS and OD
- Neurobiological assessment

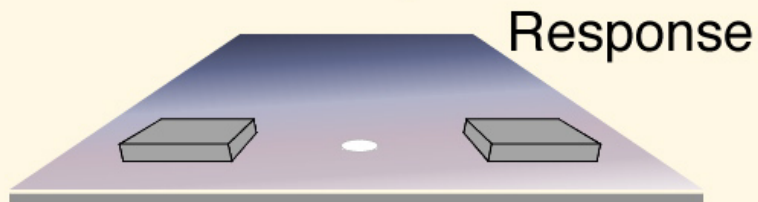
# Delayed Response

- A test of spatiotemporal working memory
- Critically requires the prefrontal cortex
- Robustly sensitive to aging

DR



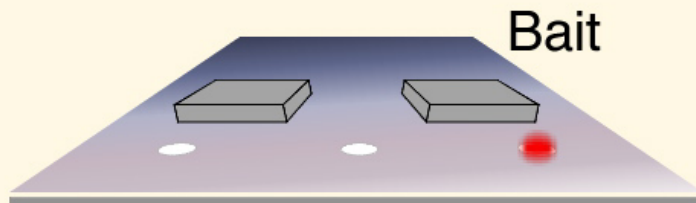
Delay



+

-

ITI



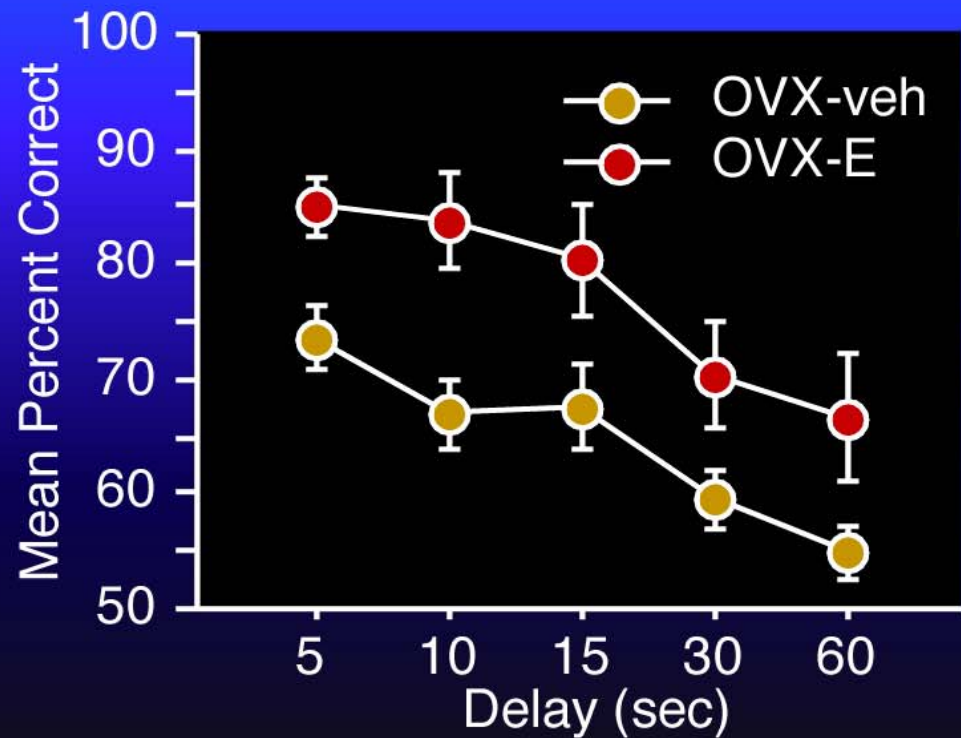
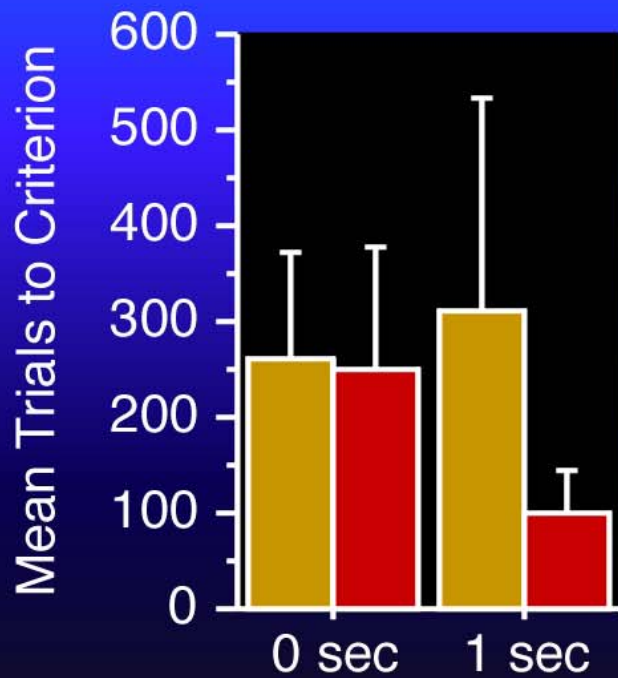
Delay



-

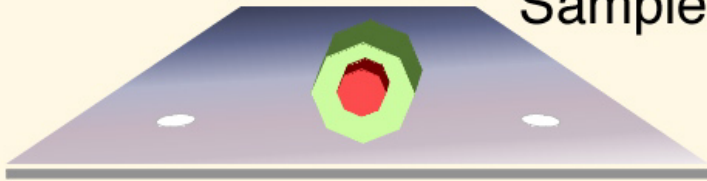
+

# Delayed Response



DNMS

Sample



+

Delay

Recognition



-

+

ITI

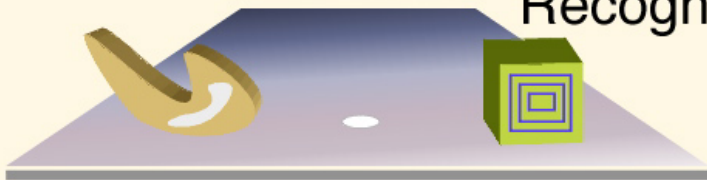
Sample



+

Delay

Recognition



+

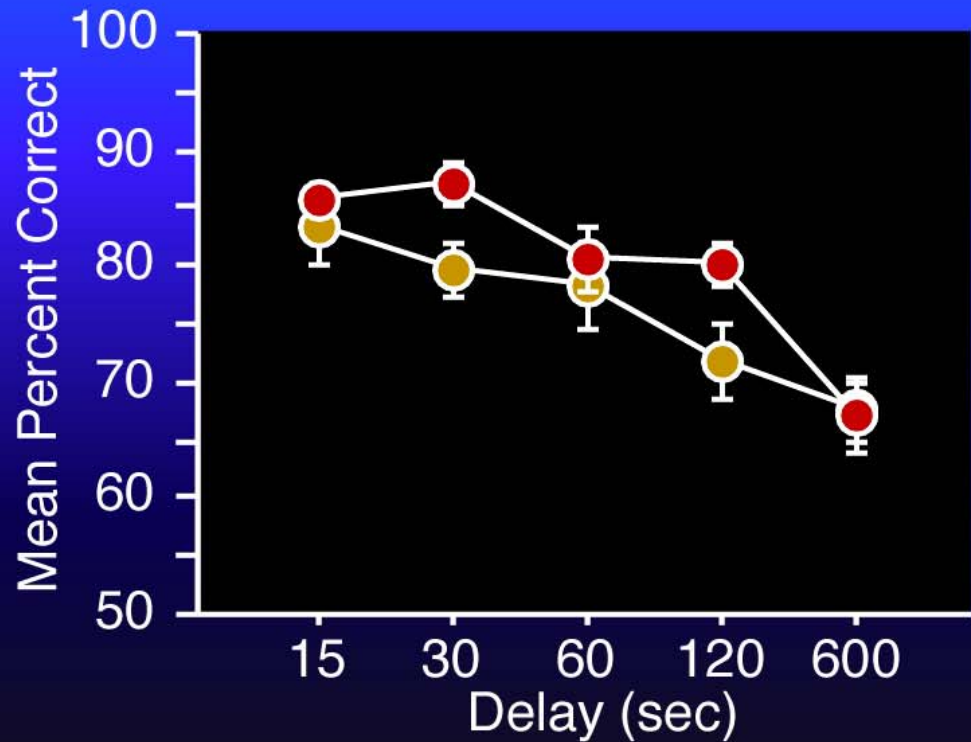
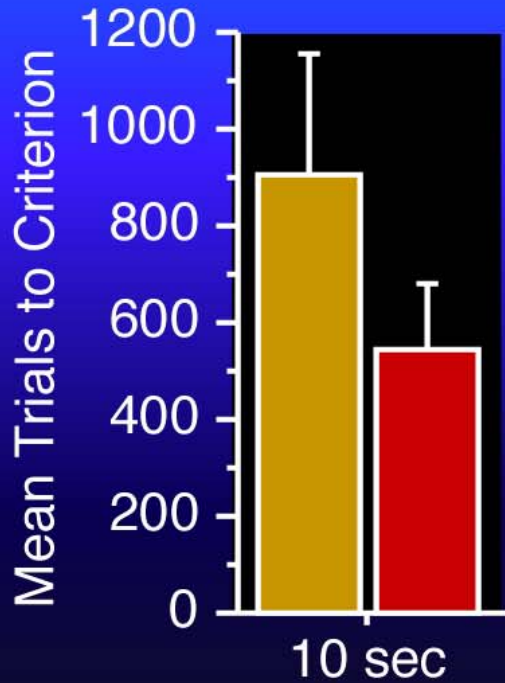
-

# Delayed Nonmatching to Sample

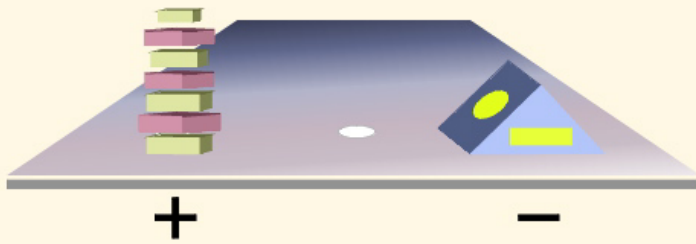
- A test of recognition memory
- Critically requires the medial temporal lobe system
- Modestly sensitive to aging



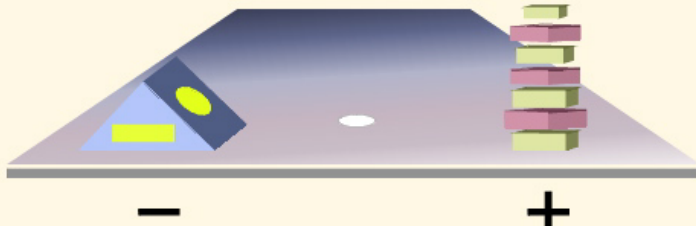
# Delayed Nonmatching-to-Sample



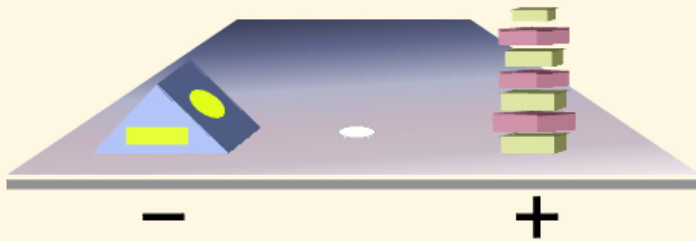
OD



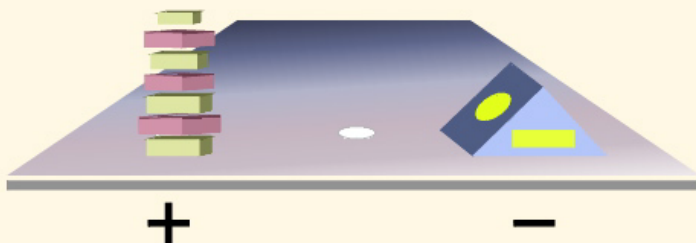
ITI



ITI



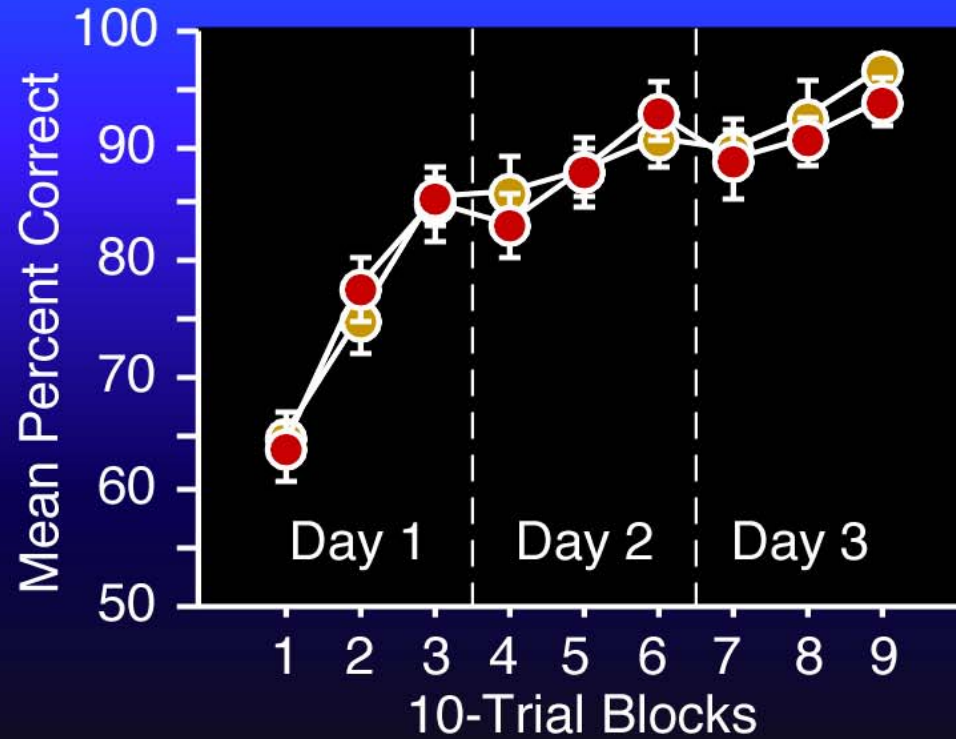
ITI



# Object Discrimination

- A test of simple stimulus-reward association learning and retention
- Modestly sensitive to medial temporal lobe damage and aging

# Object Discrimination

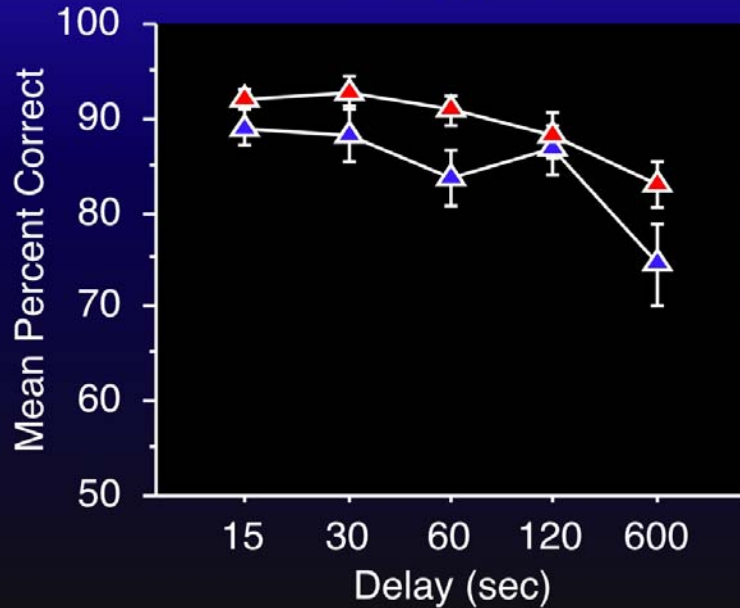
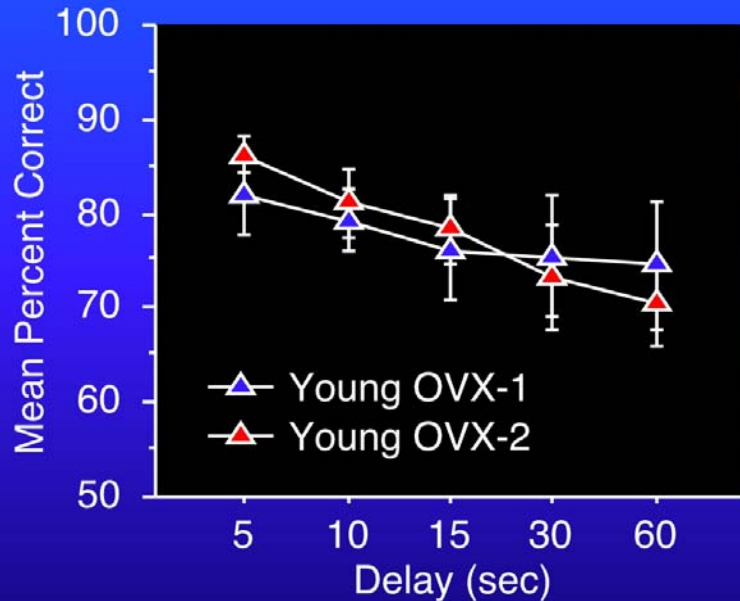


# Does aging influence the cognitive response to estrogen treatment?



# Cognitive Effects of Estrogen in Young OVX Monkeys: Interim Results

Delayed Response



Delayed Nonmatching-to-Sample

# Conclusions

- Estrogen status robustly influences the cognitive outcome of normal aging in monkeys
- The cognitive effects of cyclic estrogen treatment extend beyond memory
- Ovarian hormone influences on cognitive function may be age-dependent
- A primate model for exploring the neurobiological basis of ovarian hormone effects on cognitive aging

# Acknowledgments

Mount Sinai School of Medicine

Ying Mao

Michael Calhoun

Tracy Aiello

Jul Lea Twining

Diana Zentko

Bonnie Fletcher

Judy Choi

Erica St. Lawrence

Haydee Vercesi

John Morrison

Patrick Hof

CNPRC - UC Davis

Jeffrey Roberts

Deborah Kent

Sania Fong

Mary Roberts

Harry Arnell

Chad Ellis

Heather McKay

Carmel Stanko

Supported by  
National Institute on Aging