Hormone Therapy and Cognitive Performance - Reconciling Animal Studies with Clinical Data

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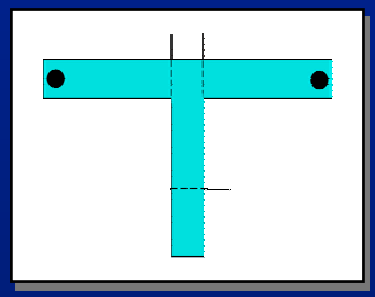
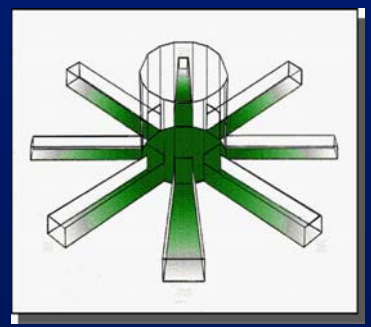
Relevance of Ovx Model

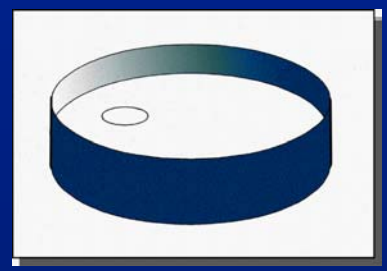
- >600,000 HTX each year in USA (Farquhar & Steiner 2002)
- 1/3 of women in USA will have their ovaries removed prior to age 60

Tasks Used to Assess Effects of Ovx and Hormone Treatment on Cognitive Performance



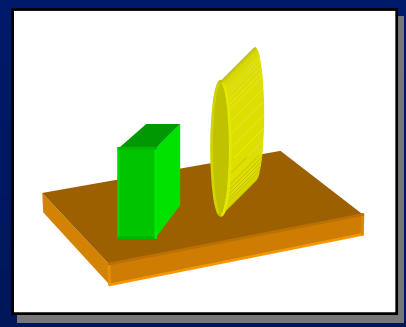
E enhances acquisition
Protects against IH scopolamine
Enhances WM, but not RM
Prevents Age-related decline in performance



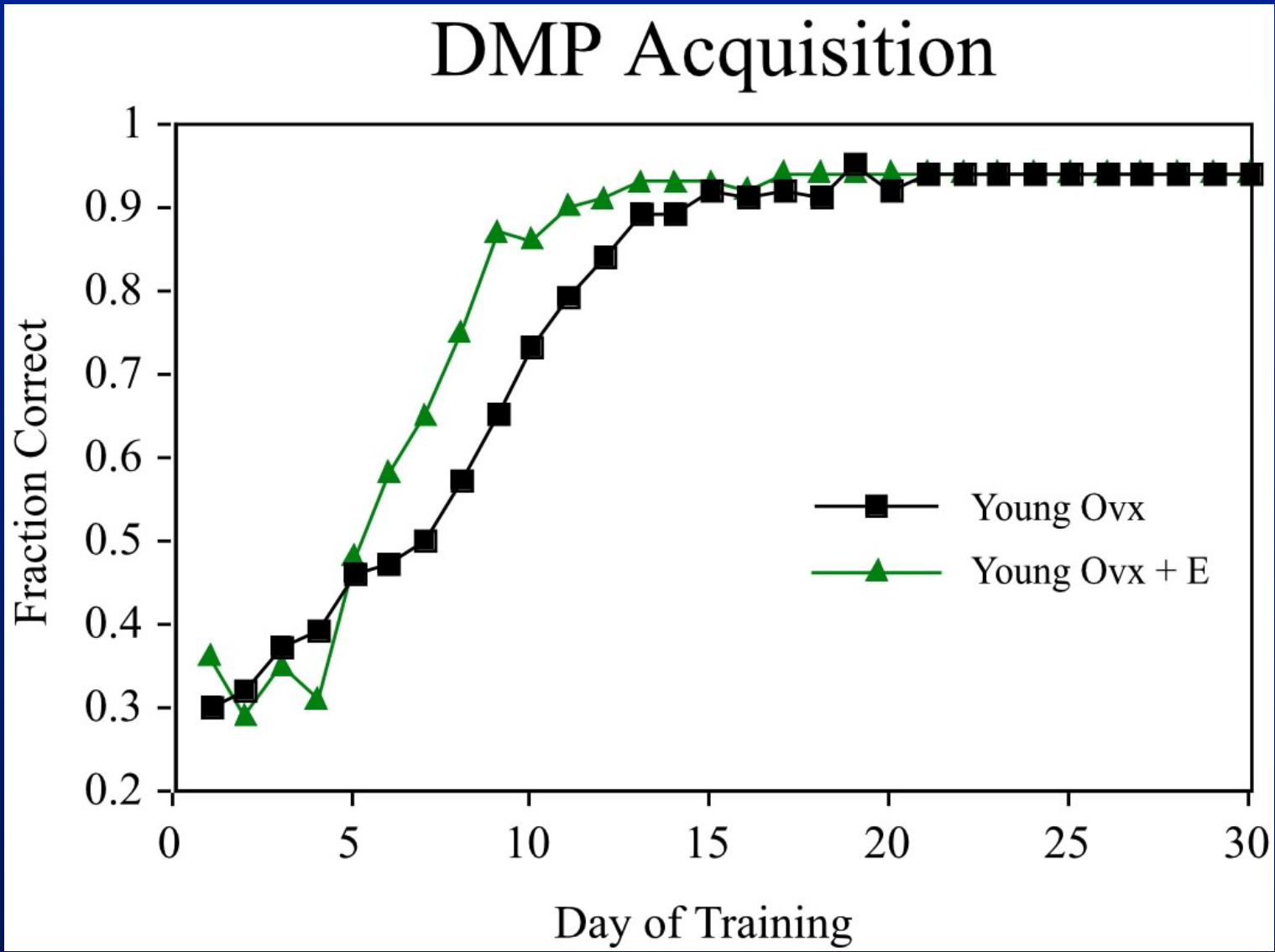


E and E+P enhance performance
on certain versions of MWM

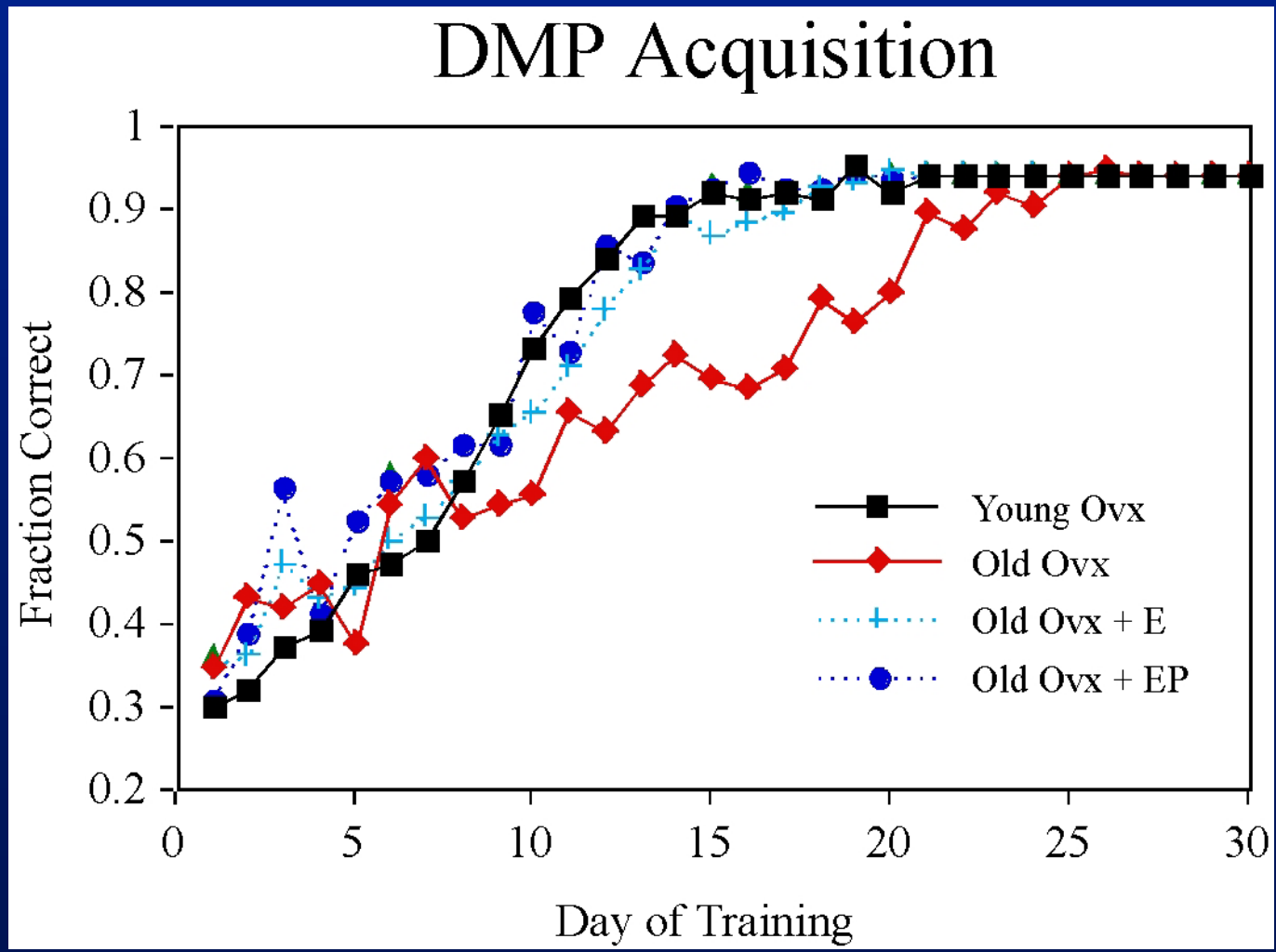
Ovx impairs OR memory. Reversed by E-Tx.



Estradiol Enhances DMP Acquisition



Hormone Treatment Can Prevent Age-Related Impairment in DMP Acquisition



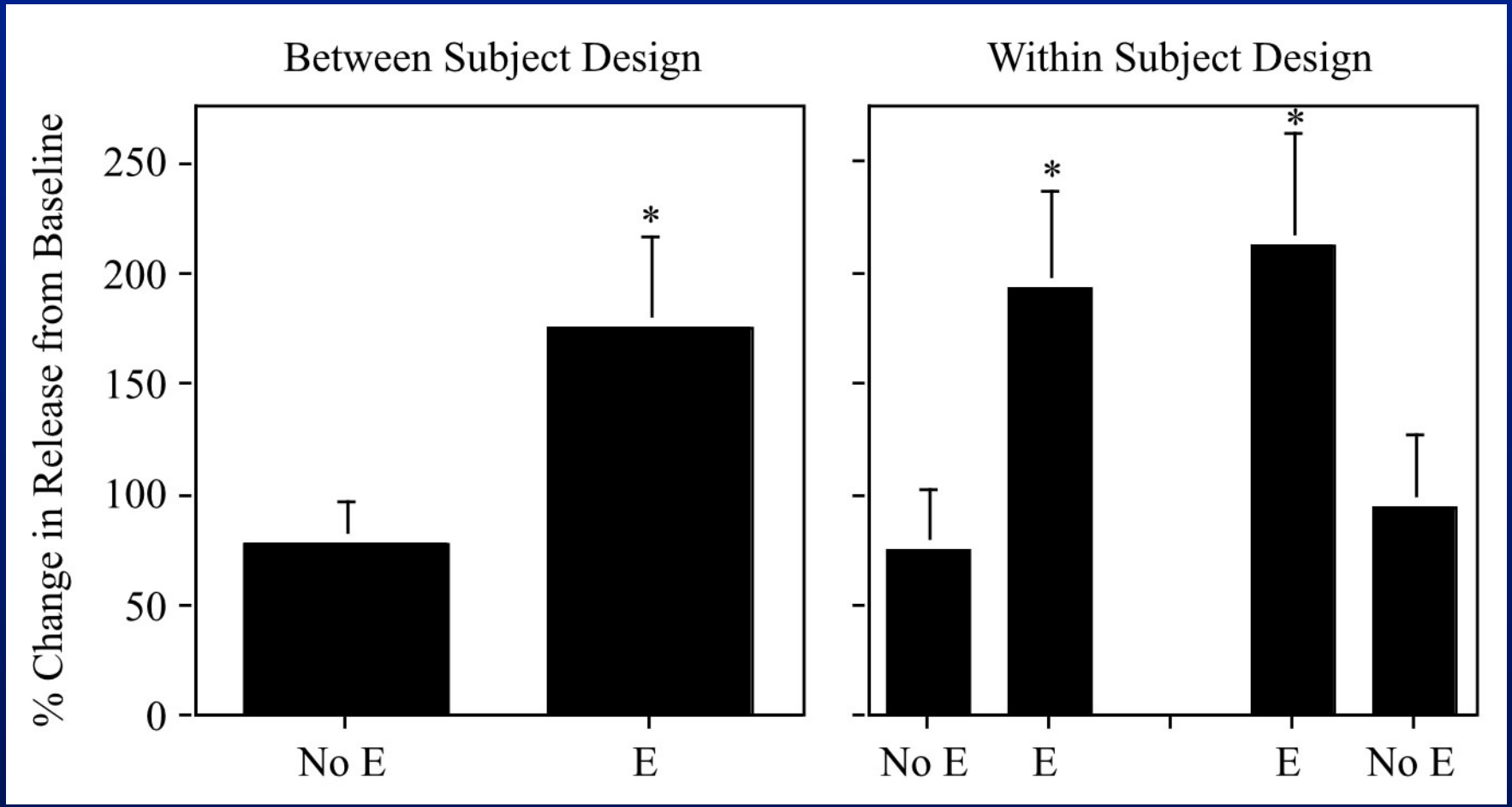
From Gibbs, Neurobiol of Aging 21, 2000

Basal forebrain cholinergic neurons play in important role in learning and memory functions and have been implicated in age-related cognitive decline

Estradiol Has Significant Effects on Basal Forebrain Cholinergic Function

- Increased ChAT expression
- Increased HACU
- Increased ACh release
- Maintenance of cholinergic fibers

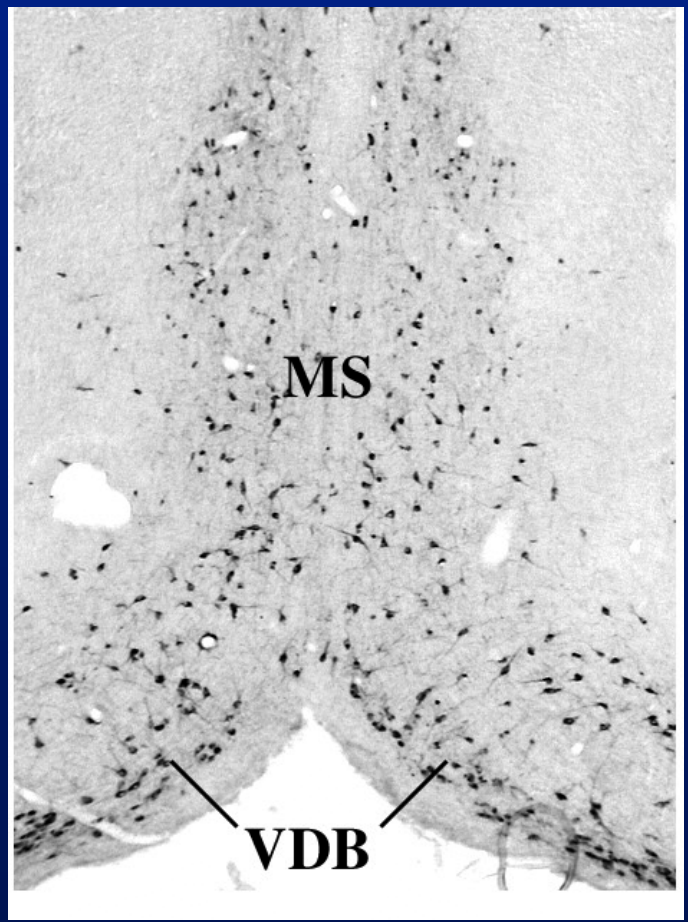
Example: Estradiol Enhances Potassium-Stimulated Acetylcholine Release



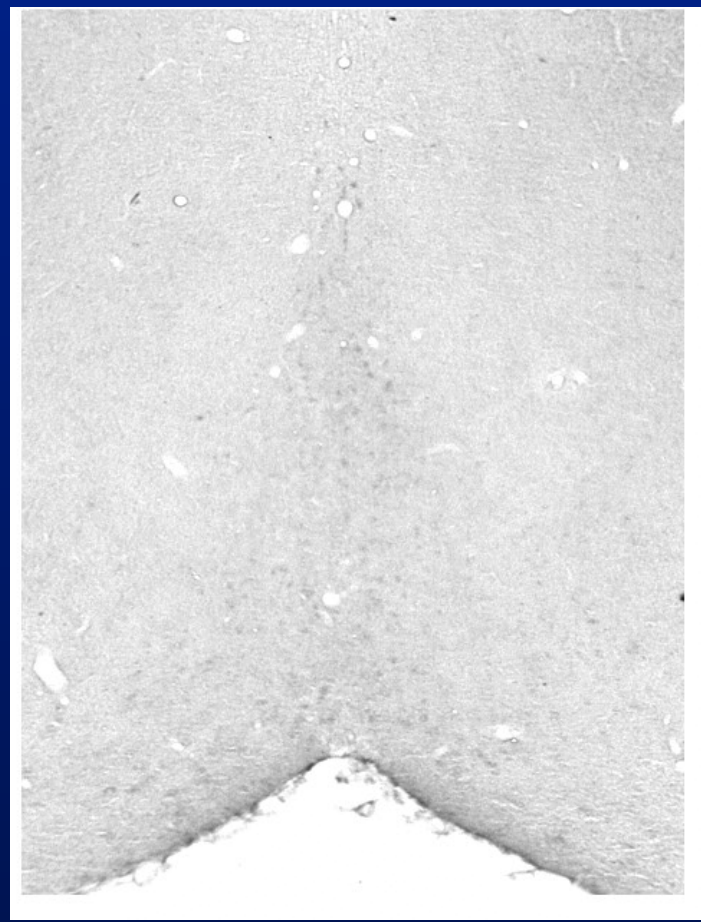
From Gabor et al, Brain Research 962, 2003

One Can Selectively Destroy BFCNs by Injecting 192 IgG-SAP

VEH

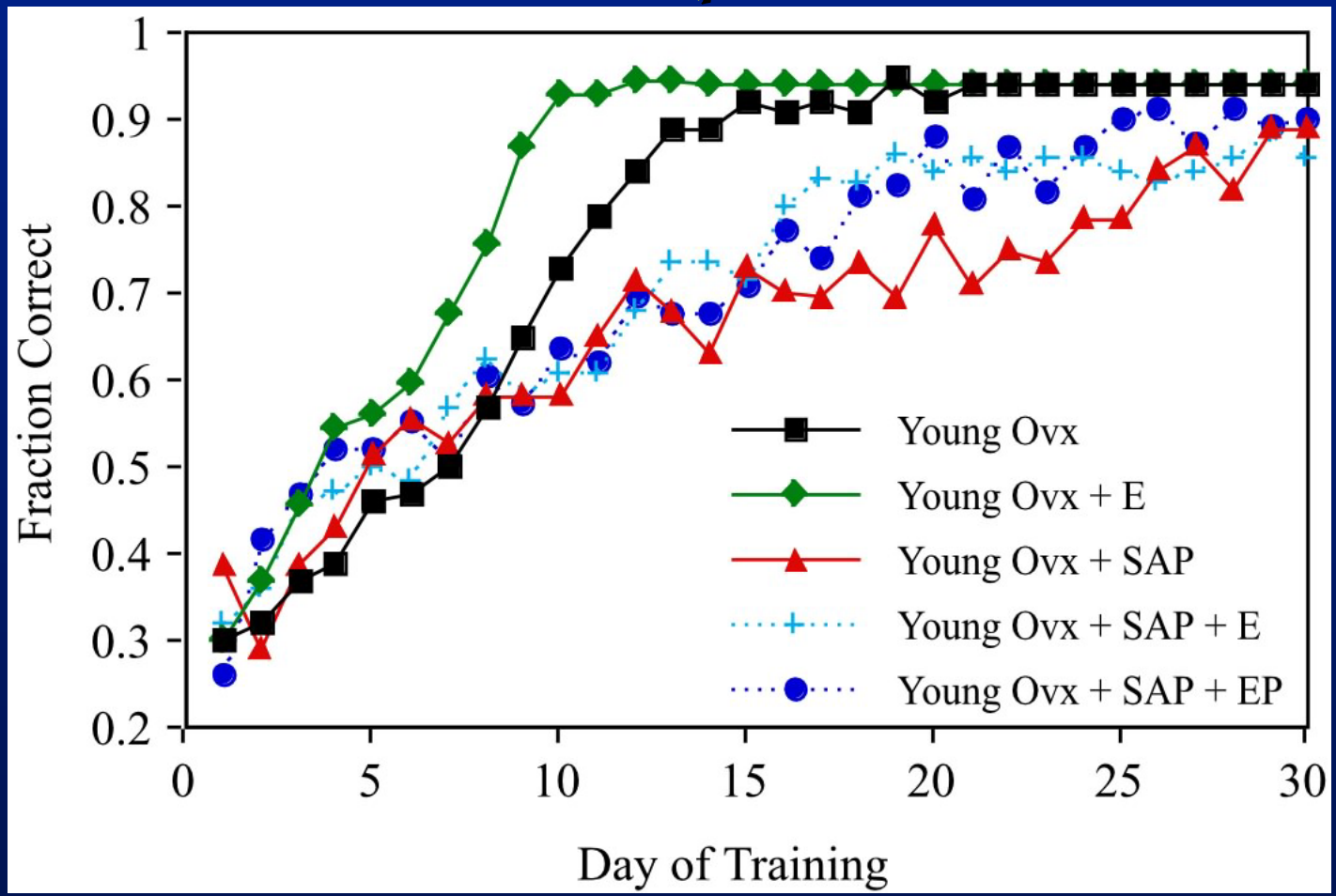


SAP



From Gibbs, Horm. & Behav. 42, 2002

Destruction of BFCNs Prevents Effects of Hormone Treatment on DMP Acquisition



From Gibbs, Horm. & Behav. 42, 2002

Estradiol Affects Hippocampal Structure and Function

- Increased spines & synapses in CA1
- Increased NMDA receptors & NMDA Responses
- Enhanced LTP
- Reduced LTD

H_1: Brought about by a reduction in GABA-mediated inhibition of pyramidal neurons, leading to increased CA^{++} entry via NMDA receptors, activation of PKA, MAPK, CaMKII, & CREB.

Temporal pattern of change in CA1 pyramidal cell spine density matches alterations in memory duration (Sandstrom & Williams, 2001). This suggests that effects on spine density (I.e., hippocampal function) play a role in effects on cognitive performance.

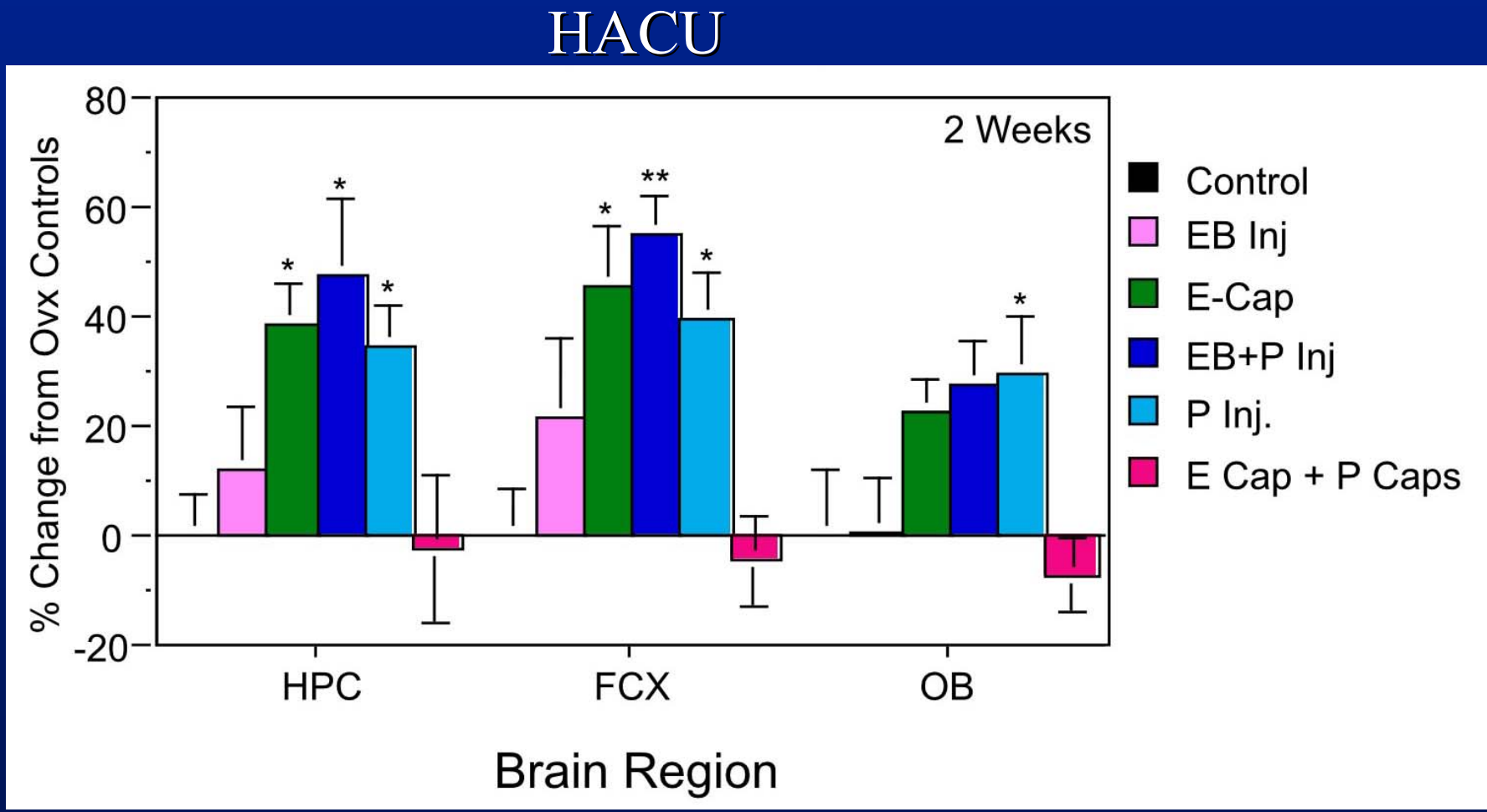
Effects on hippocampal structure and function RELY UPON basal forebrain cholinergic inputs!

Rudick et al. 2003
Lam & Leranth 2003
Daniel & Dohanich 2001

How does this relate to clinical studies, and to the WHIMS specifically?

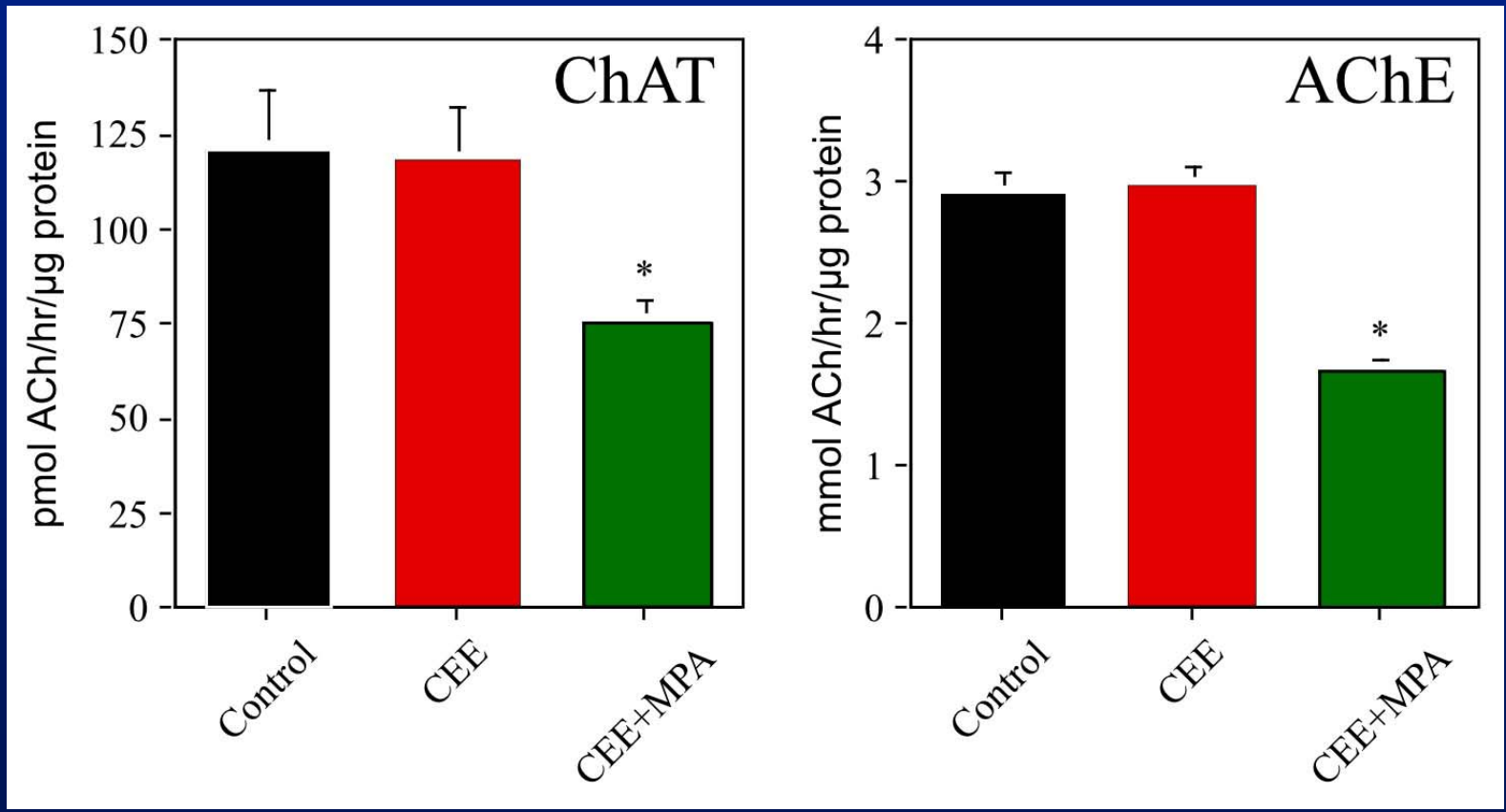
Effects on cholinergic measures depend on timing, dose, regimen, and duration of treatment

Different Regimens of Hormone Treatment Have Different Effects on HACU



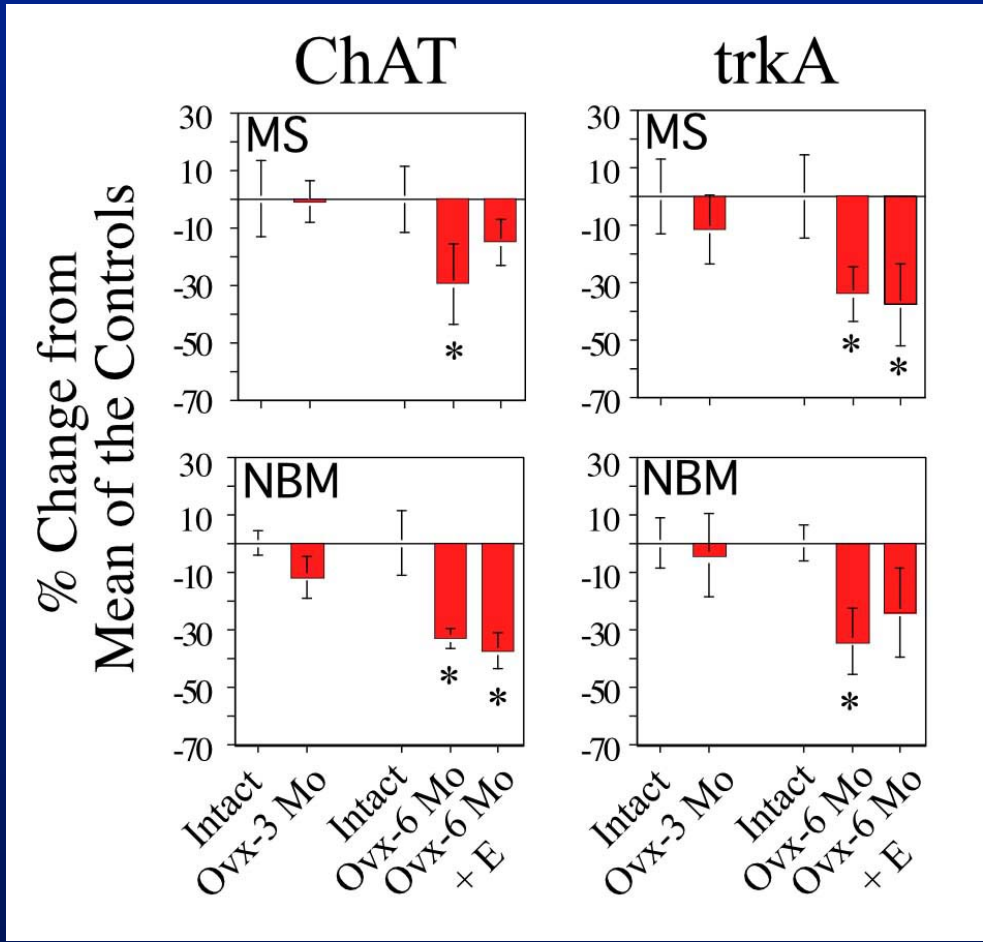
From Gibbs, Neurosci. 101, 2000

Long-Term Treatment with CEE and CEE+MPA Reduces ChAT and AChE in the MS/DB of Cynomologous Monkeys



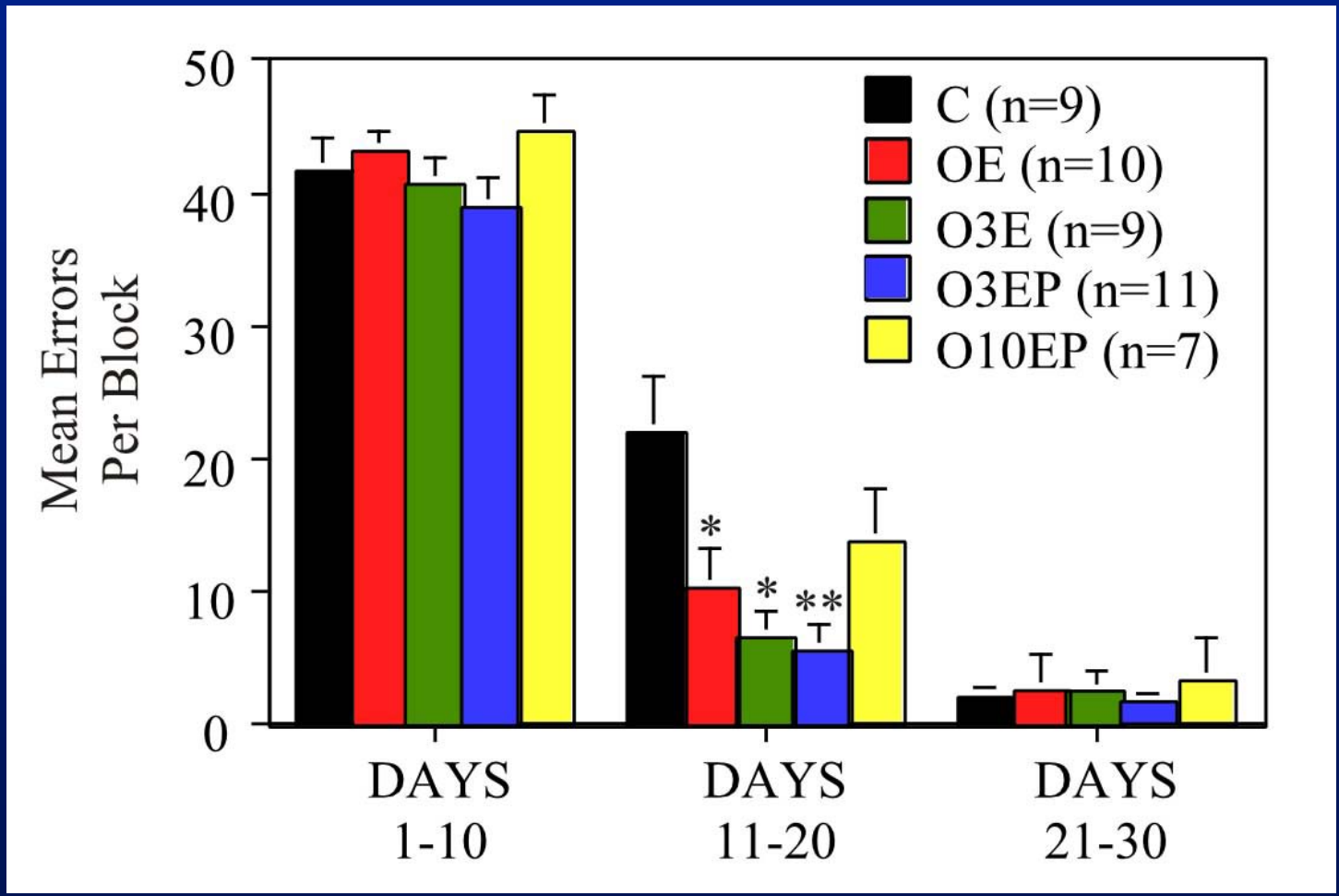
From Gibbs et al, Neurosci. 113, 2002

Ovx Decreases Cholinergic Measures Beyond the Effects of Normal Aging



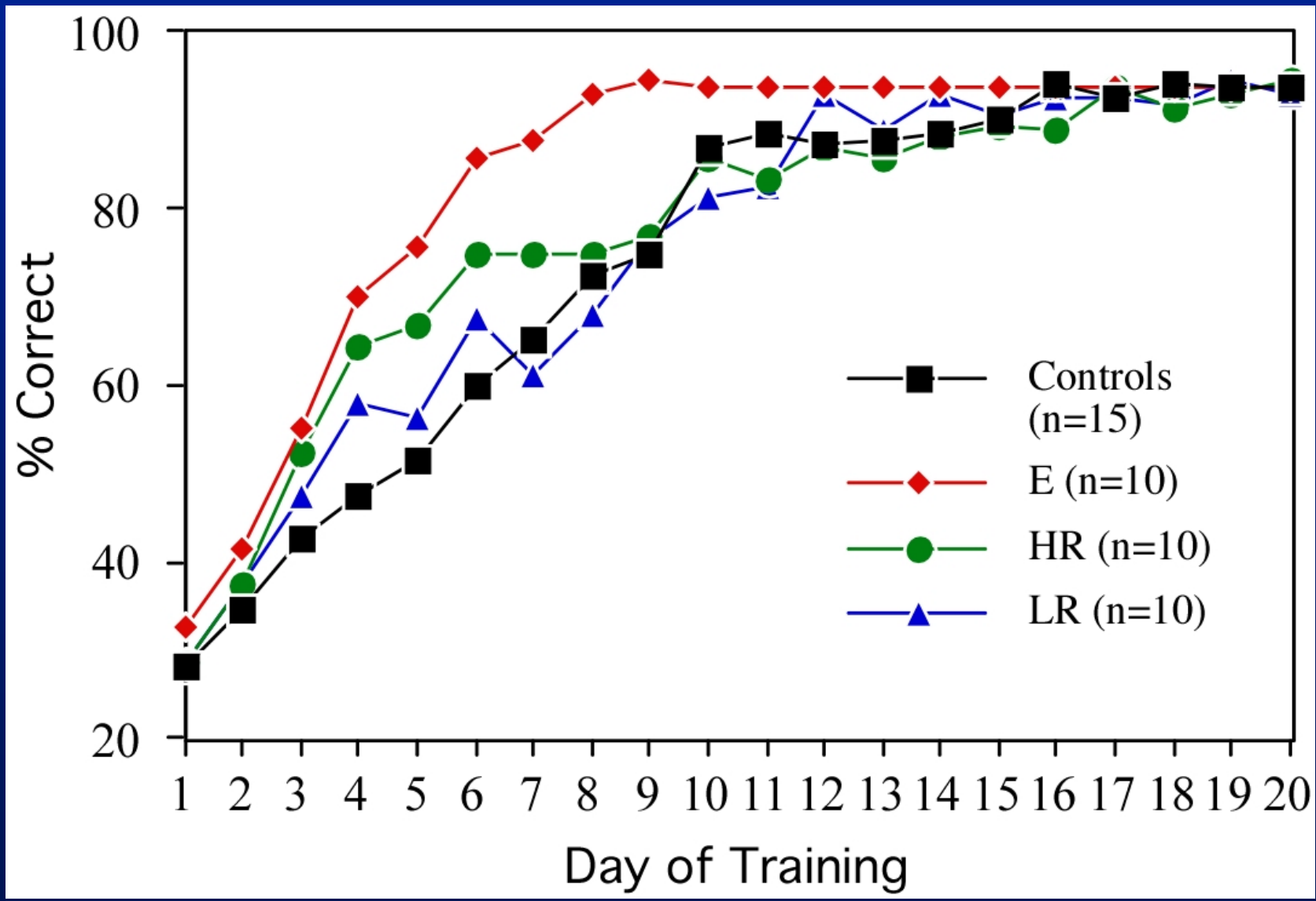
From Gibbs, J. Neuroendocrinol. 15, 2003

Effects on DMP Acquisition in Rats Diminish with Ovx and Aging (Window of Opportunity)



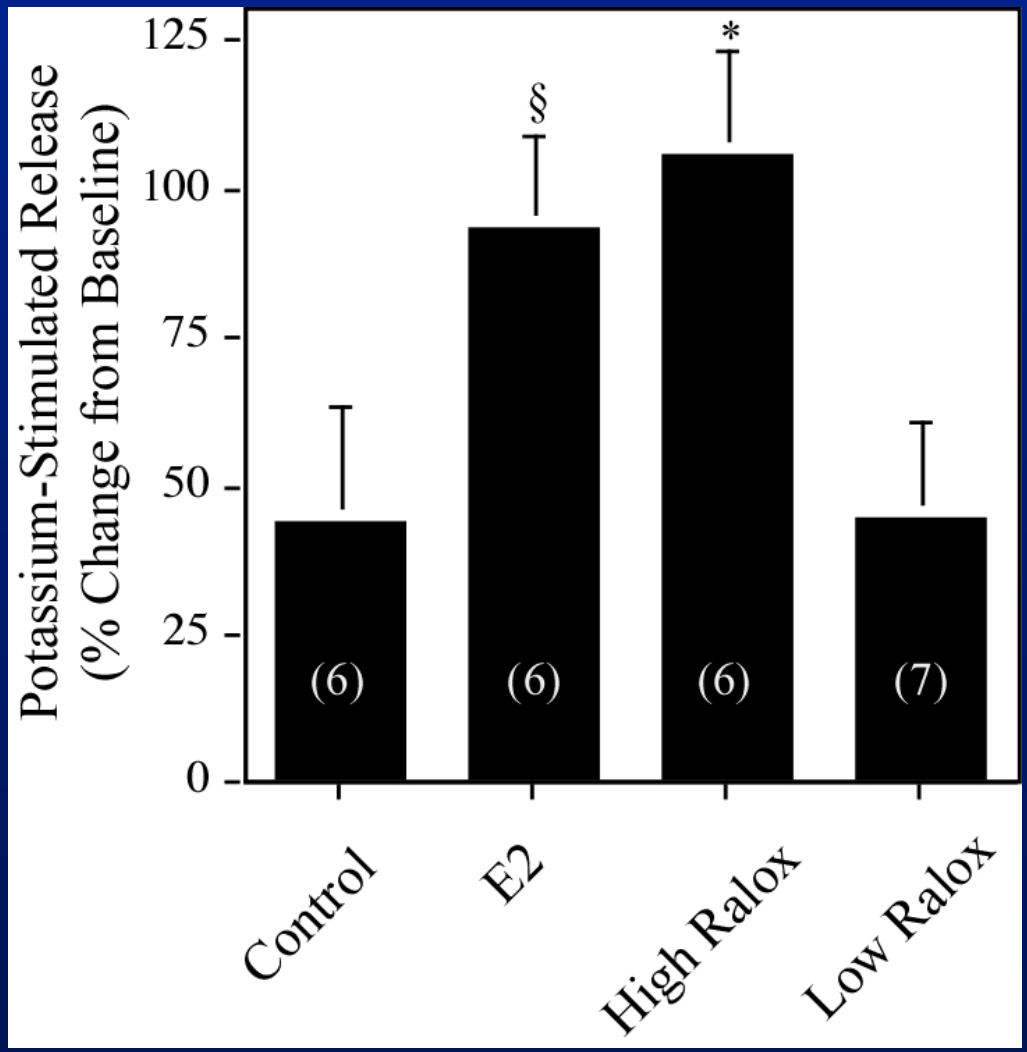
From Gibbs, Neurobiol of Aging 21, 2000

Raloxifene Acts as a Partial Agonist



From Gabor et al., Psychoneuroendocrinol, 29, 2004

Raloxifene Can Increase Potassium-Stimulated ACh Release



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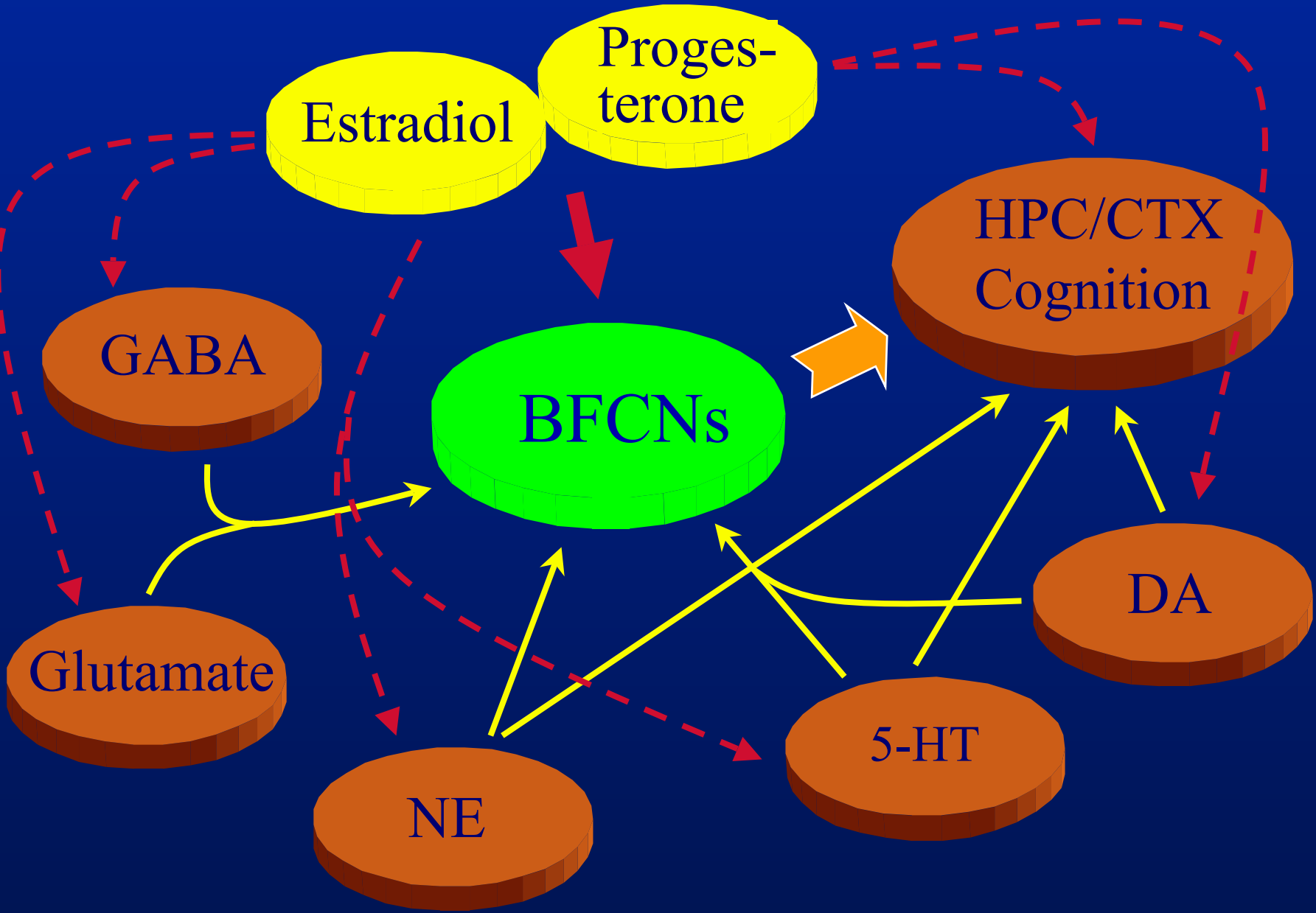

Conclusions

The brain is not a uterus, it is not a breast, or a bone

- Therapy for the brain must be tailored to the brain.
- Under appropriate conditions, hormone therapy can enhance performance within specific cognitive domains and help prevent age-related cognitive impairment.
- In the rodent, BFCNs play an important role in mediating effects of hormone therapy on hippocampal function and cognitive performance.
- Results depend on dose and regimen, as well as on timing with respect to age and loss of ovarian function.