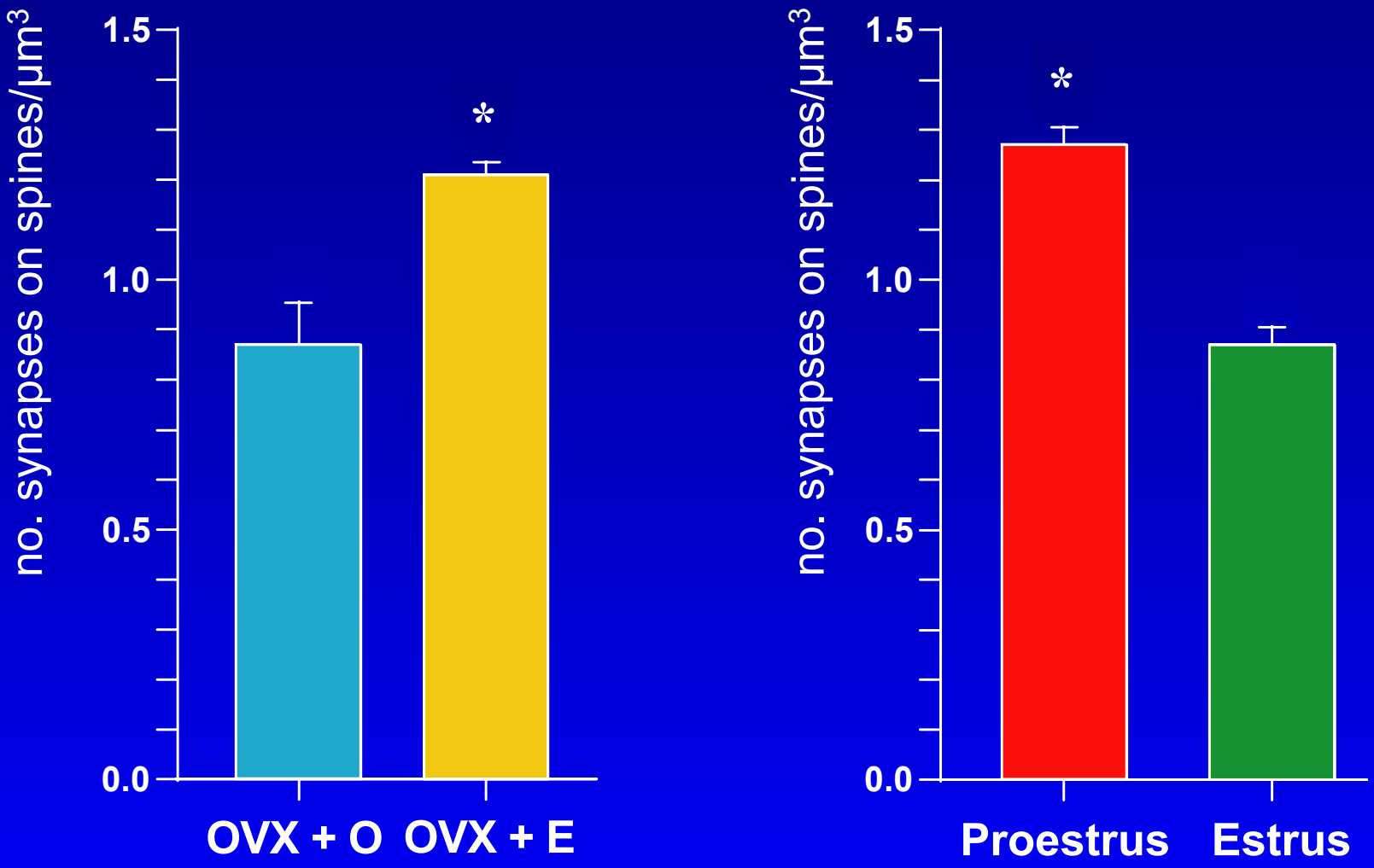
Estrogen and the Aging Cortical Synapse: Implications for Cognitive Effects in Aged Monkeys.

John H. Morrison, Ph.D.

Rat and monkey studies suggest that age-related synaptic alterations occur in hippocampus that are circuit and cell class-specific.

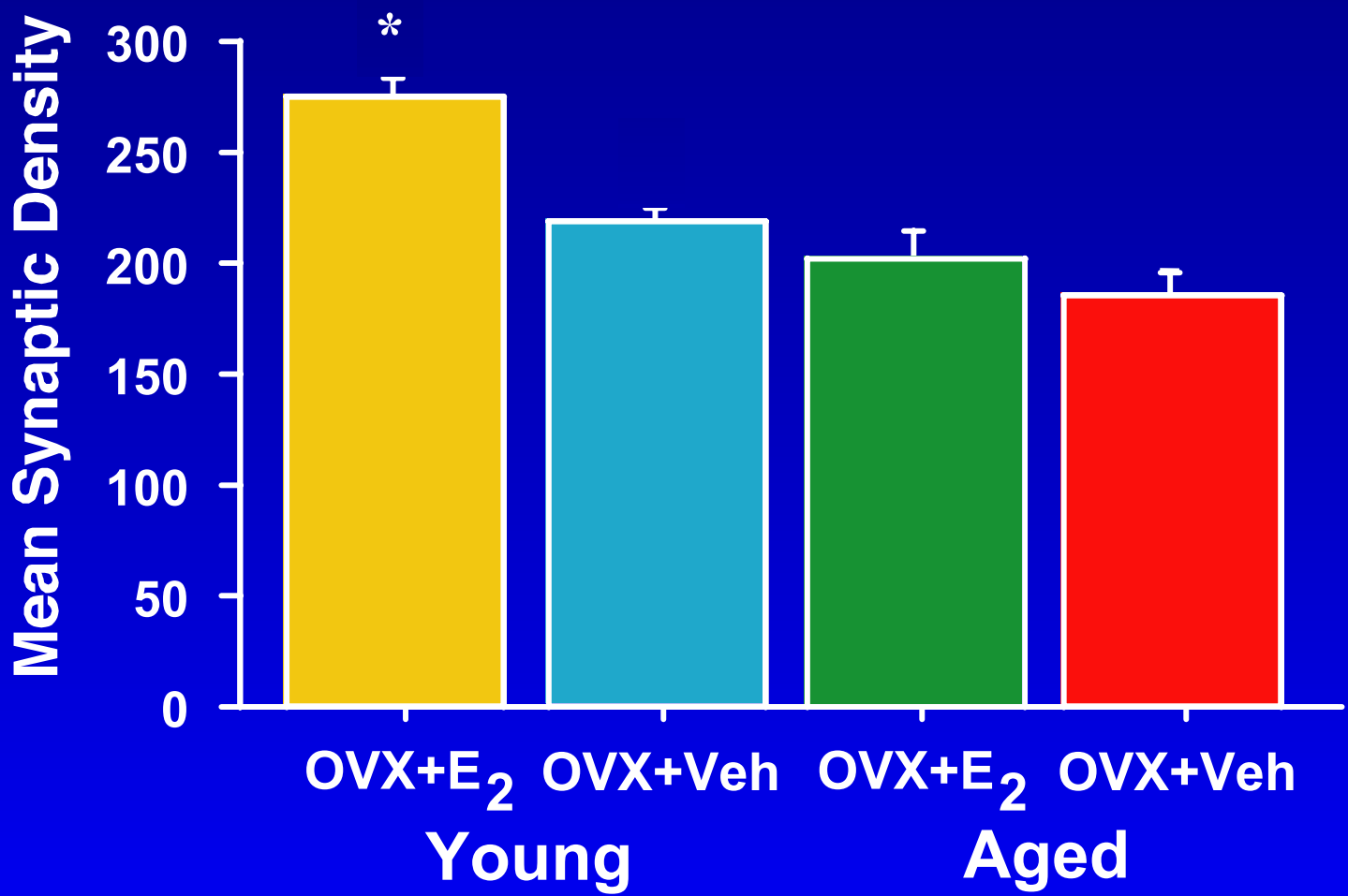
Estrogen affects CA1 synaptic organization . Does it also affect neocortical areas vulnerable to aging? How do endocrine effects on these circuits interact with neural aging?

Estrogen Regulates Density of Axospinous Synapses in young female rats



Gould et al., J. Neurosci. 1990
Woolley and McEwen, J. Neurosci. 1992

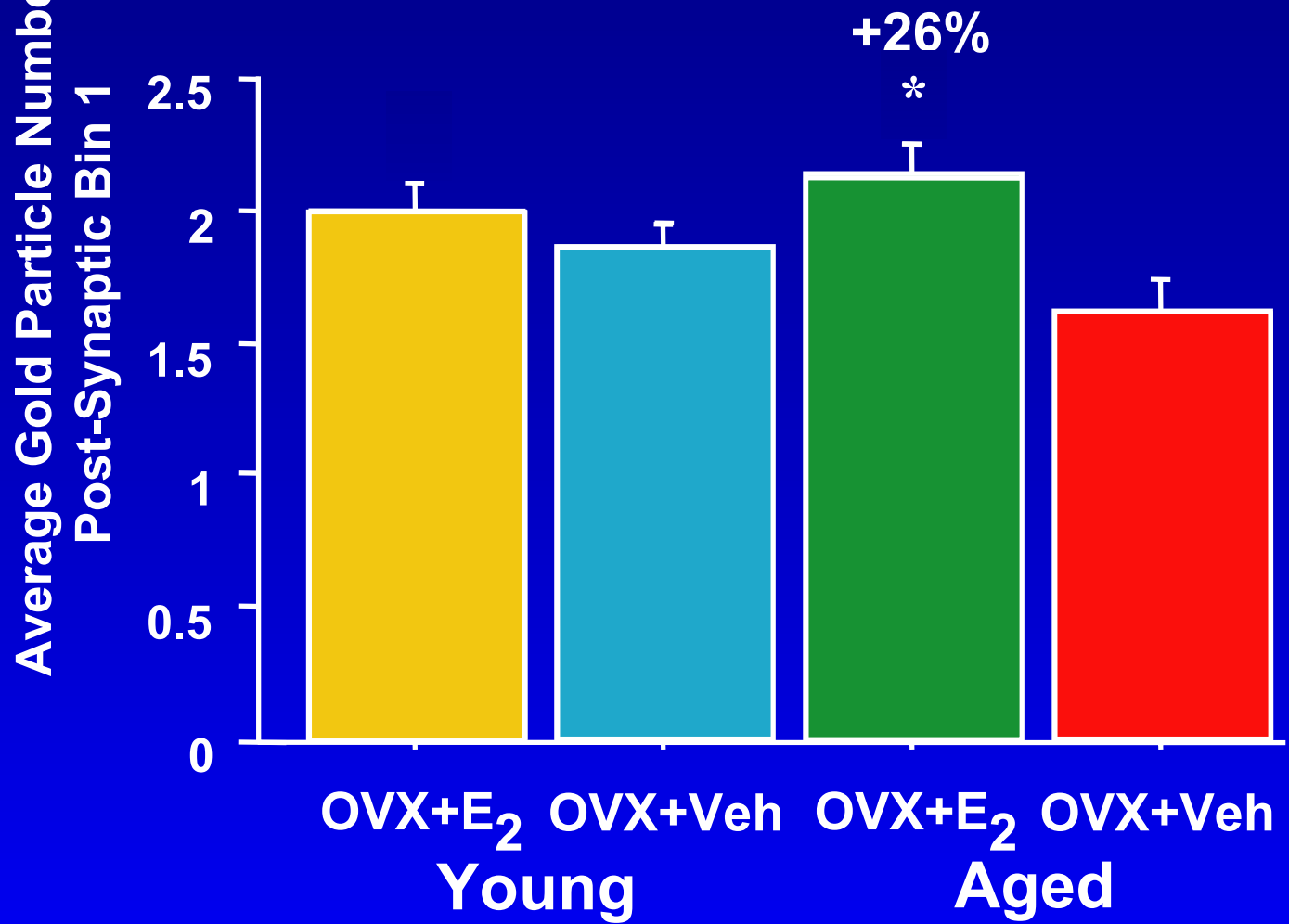
Mean Axospinous Synapse Density CA1 Stratum Radiatum: There is an age-related decrease that is not reversed by E.



* p < 0.005

Adams et al, PNAS, 2001

Synaptic NMDAR1 is increased by E in CA1SR of aged rats



* p < 0.05

Adams et al, PNAS, 2001

Additional EM immunogold findings:

A) ERα (Adams et al, J. Neurosci. 2002)
   1) present pre-and post-synaptically in 30% of axospinous synapses in young CA, but 15% in aged CA1
   2) pre-and postsynaptic levels down-regulated with E in young CA1, but not responsive in aged CA1

B) NR2A and NR2B (Adams et al., J. Comp. Neurol. 2004)
   1) no effect of E on synaptic NR2A and NR2B in young CA1 (consistent with NR1), but NR2B increases in lateral portion of synapse in aged CA1, possibly reflecting active molecular plasticity.

Summary: Estrogen effects on excitatory synapses in CA1 of female rat

Thus, while E impacts the synaptic NMDAR profile in CA1 of aged female rats (i.e., molecular plasticity), it does so in the context of compromised capacity for structural plasticity.

The failure of structural plasticity may be related to the decreased synaptic ER-α in CA1 that occurs with aging.

Estrogen, spines, aging, and behavior

What about monkeys?

What about neocortex?

Does estrogen impact the cognitive functions affected by aging in monkeys?

Rhesus Monkey model :

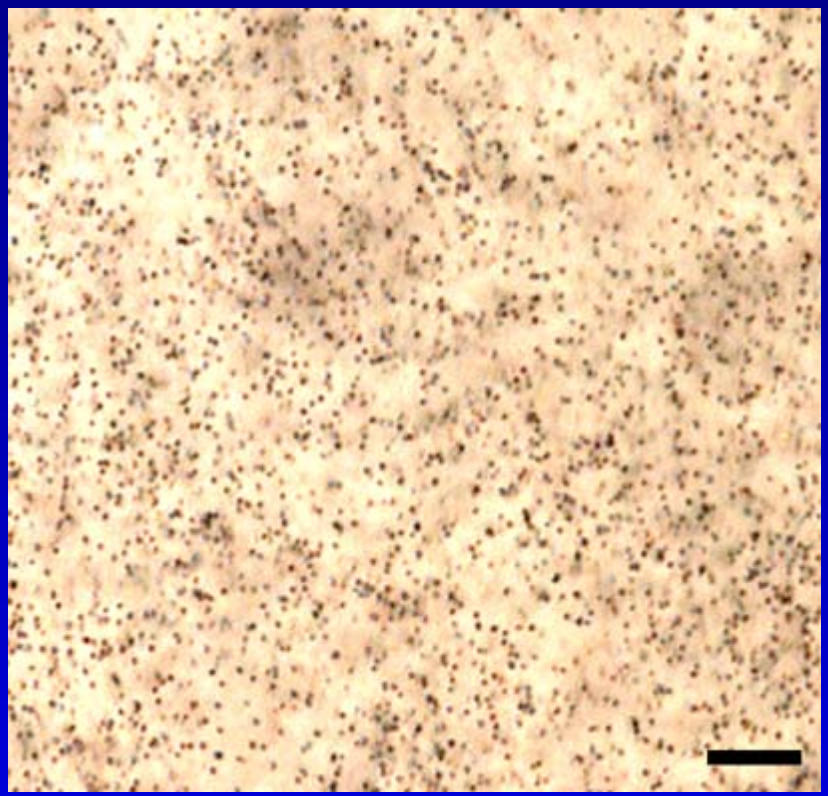
A) Treatment regimen: OVX; minimum 6 weeks post-OVX (longer for behavior group); 100ug estradiol cypionate by injection every 3 weeks (i.e., unopposed and cyclical)

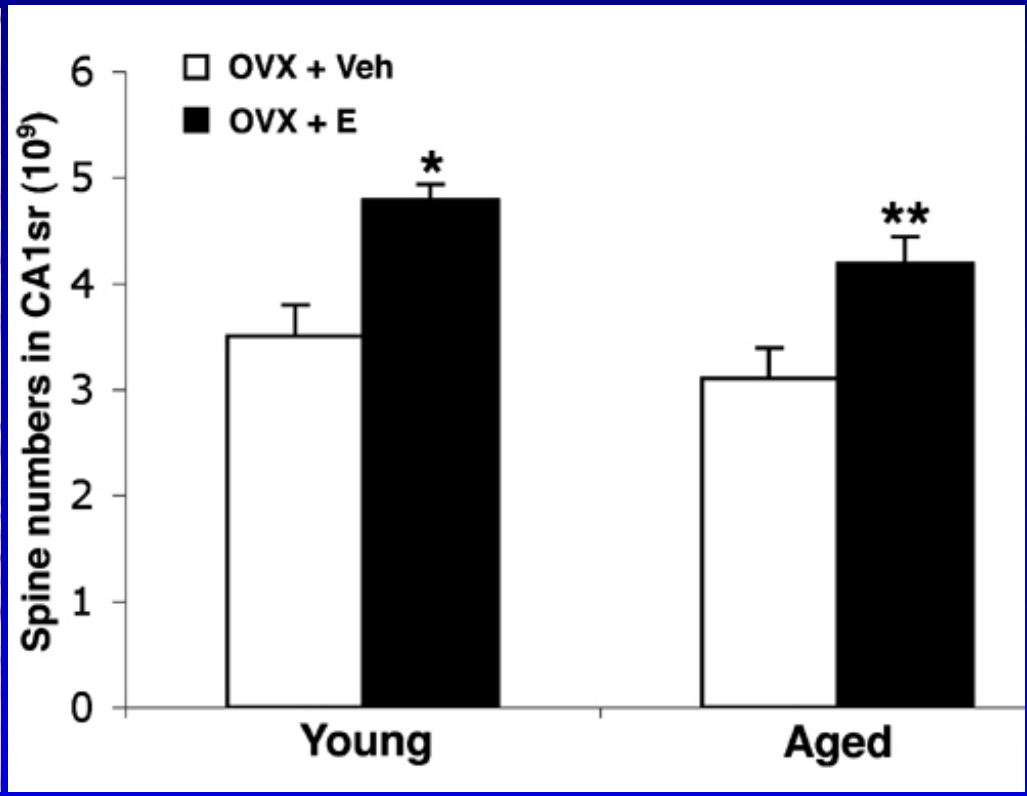
B) Morphology only: 2 cycles of inj., perfused 24 hours after 2nd inj.
1) Spines in hippocampus of young and aged monkeys (Hao et al., *J. Comp. Neurol*., 2003)
2) Spines in prefrontal cortex of young monkeys, (Tang et al.,*Cerebral Cortex*, 2004):

C) Neuropsychological analyses: (same treatment, but for 2-2.5 yrs)
1) DNMS and DR analyses of aged monkeys, OVX+E (Rapp et al. *J. Neuroscience*, 2003).

D) Microscopic studies on brains from behavioral-aged group:
1) axospinous synapse density in CA1
2) dendritic morphology and spine number in PFC

Stereologic analysis of spine number in a designated region/layer using anti-spinophilin as a marker.



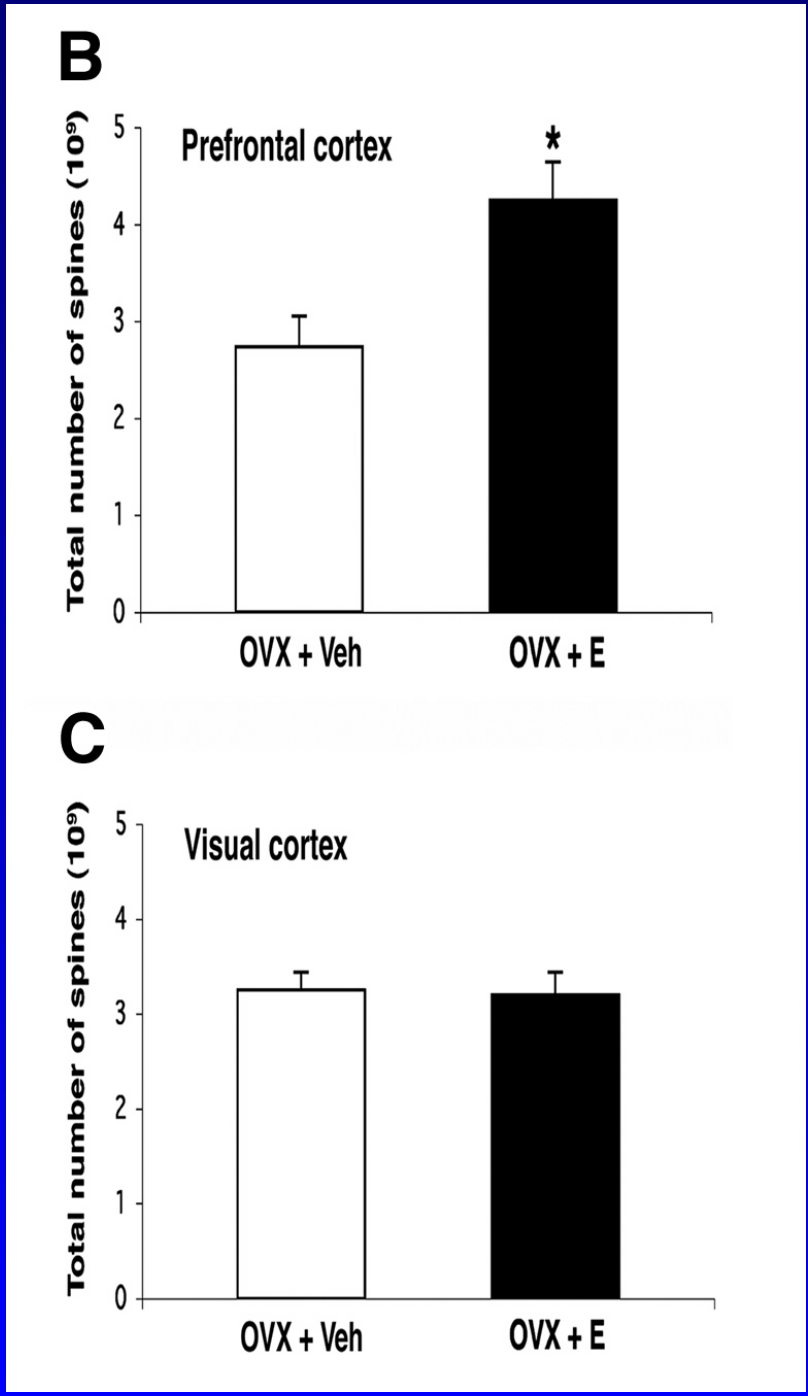


Unlike rat, spine number was increased in aged as well as young CA1. The E-induced increase amounts to 1 billion spines.

CA1 volume was unaffected and DG sp-ir spine number showed same trend, but did not reach significance.

SP-ir spine number in neocortex

In young rhesus monkeys, E-induced a dramatic increase in SP-ir spine number in Layer 1 of PFC (area 46), with no effect in V1. For technical reasons, layers II-VI could not be individually analyzed.



Early morphologic results on behaviorally characterized aged rhesus monkeys suggest:

1) Unlike aged rodents, there is an E-induced increase in synapse density in CA1 of aged monkeys.

2) Neuronal reconstructions in area 46 of prefrontal cortex show an increase in spines that may be related to the E-induced cognitive enhancement seen in these monkeys.

General Conclusions from Non-human Primate Studies

The cognitive effects of E treatment in aged monkeys were more robust for DR than DNMS and this is supported by morphologic data. This reinforces the importance of PFC for age-related cognitive decline and E treatment in humans, and suggests that certain aspects of age-related cognitive decline and related synaptic alterations are amenable to intervention.

Importantly, these animals were treated with a cyclic regimen of unopposed E for 2-2.5 years, suggesting that the positive effects of such a regimen can be sustained over months and years. This has important implications for the design of replacement regimens for humans.

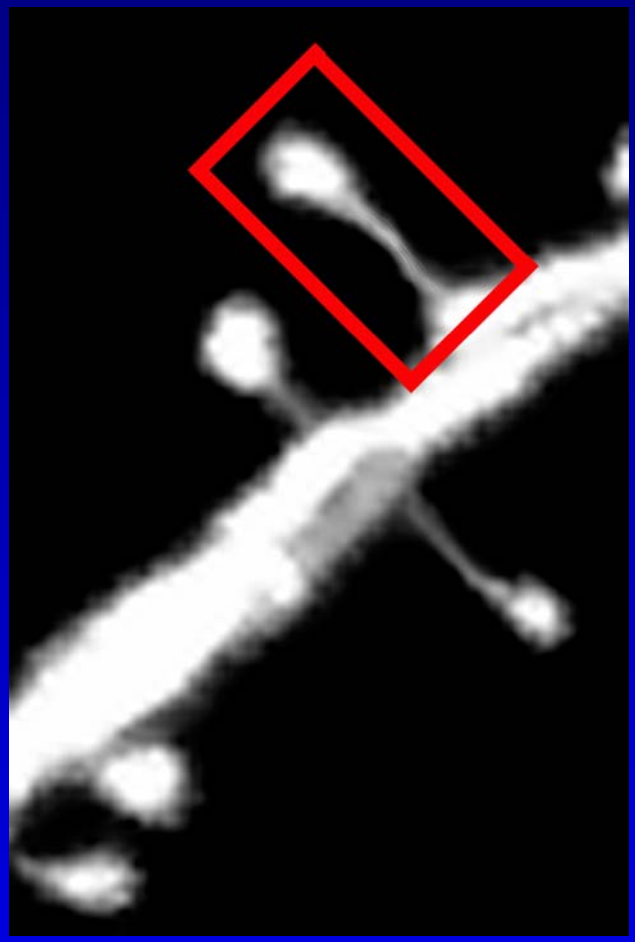
ACKNOWLEDGEMENTS

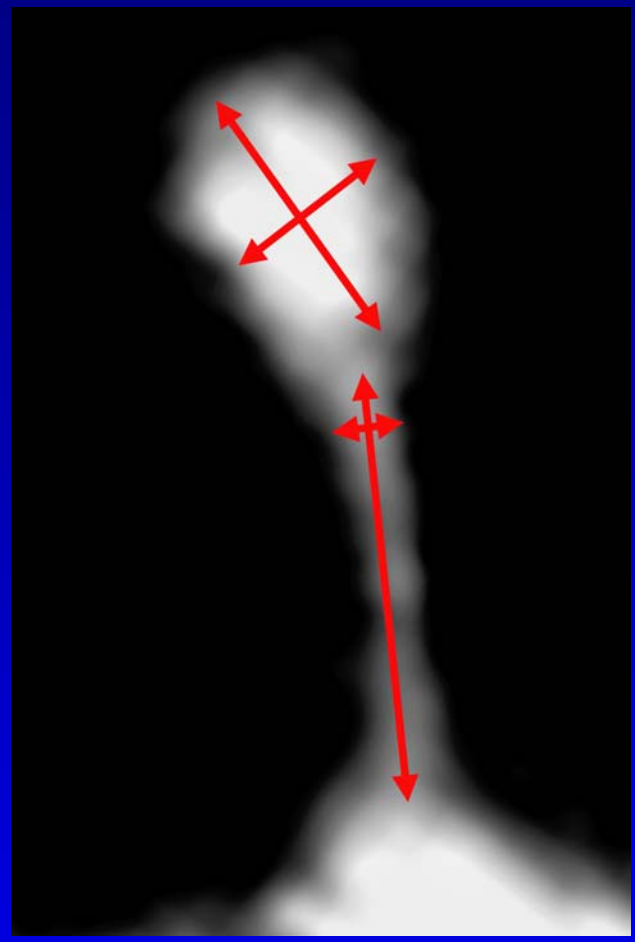
Michelle Adams
Jiandong Hao
Yong Tang
William Janssen
Ravi Shah
Susan Fink
Ginelle Andrews
Murat Yildirim

Patrick Hof
Peter Rapp
Bruce McEwen
Teresa Milner
Jeffrey Kordower
Andrea Gore
Jeff Roberts
Heather McKay
Bill Lasley
Paul Greengard
Patrick Allen

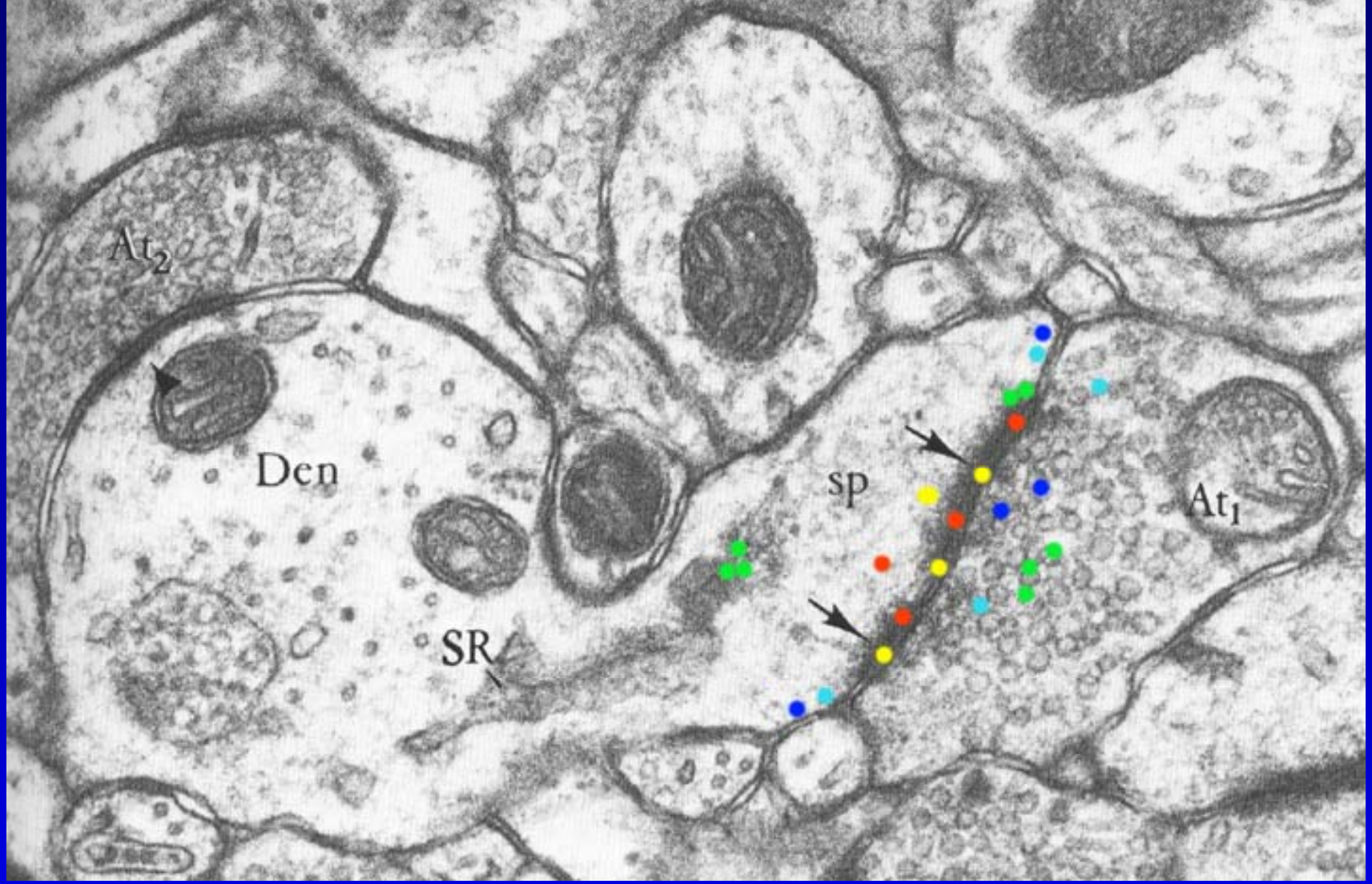
Funded by NIA

Spine morphology





The same 3-D confocal reconstructions are deconvolved, and imported to Vias. Single spines are sampled for head diameter and length, and neck diameter and length. Thus far, 10 spines from each of 9 animals (90) have been analyzed.



NR1 GluR2 EAAC1 mGluR1 ER-α