Andrus Gerontology Center

Dept Biological Sciences

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Caleb Finch:

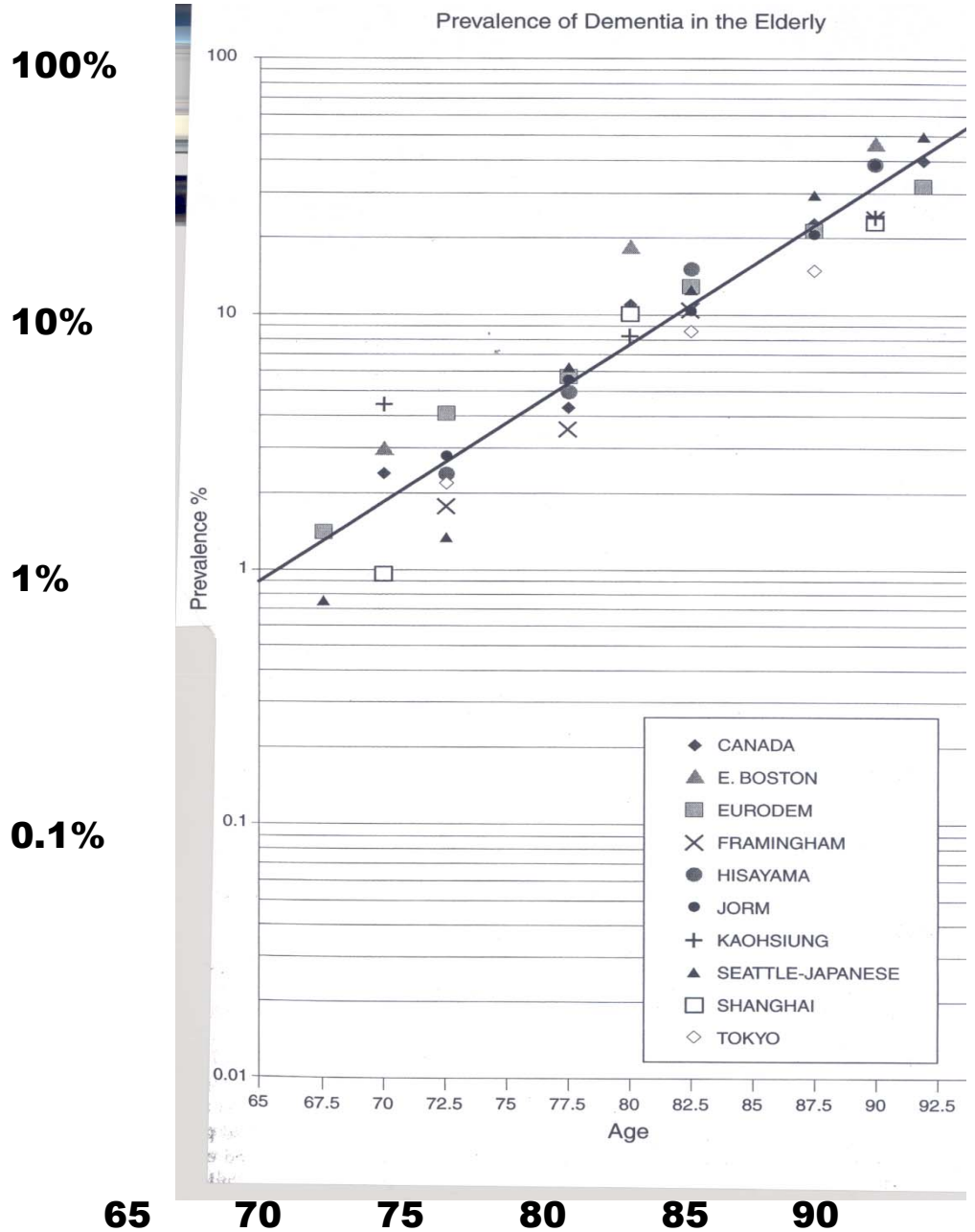
NIA Workshop 'Bench to Bedside: Estrogen as a Case Study'
Sept 28-29, 2004

"Ovarian steroids, neuroinflammatory responses, & aging"

Dementia prevalence
aging accelerates
doubles each 5 yrs

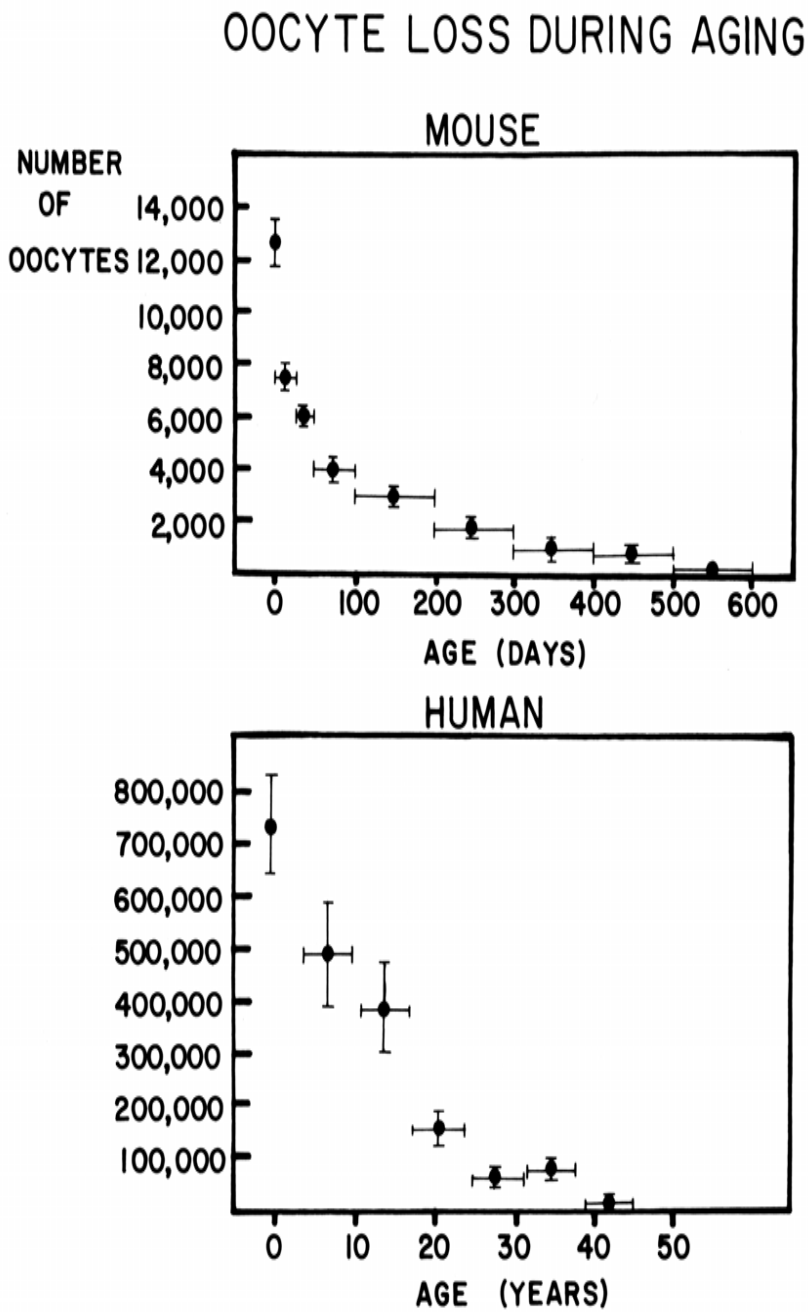
By age 70 in US,
10% cognitive
impairment

expected remaining life
with cognitive impairment
women>men, because of
greater life expectancy
Suthers et al J Gerontol, 2003



universal ovarian aging:

>95% estrogen loss at midlife precedes acceleration of dementia by 10 yrs



Shared inflammatory mechanisms?

Finch CE Neurobiol Aging, in press

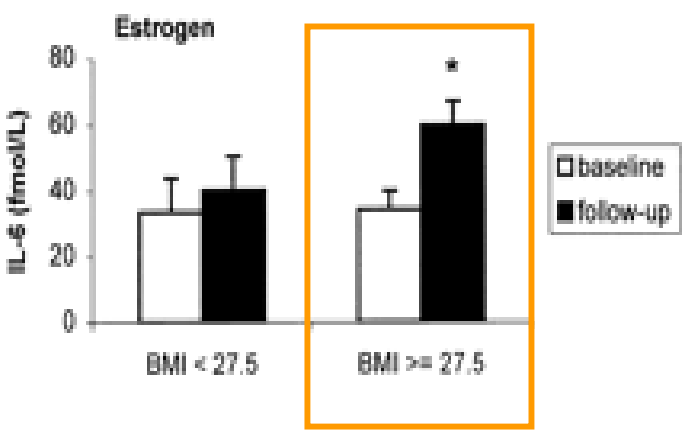
	atheroma	senile plaque
cells		
macrophages (CD68)	+++ (foam cells)	++ (microglia)
T helper (Th1)-cells	++	0
mast cells, platelets	++	0
neovascularization	++	+
proteins		
amyloids	++	++
Ạbeta	? (platelet APP)	+++
C-reactive protein (CRP)	++	+
serum amyloid P (SAP)	++	++
clotting factors	++	0
complement: C3, C5b-9	++	++
cytokines: IL-1, IL-6	++	++

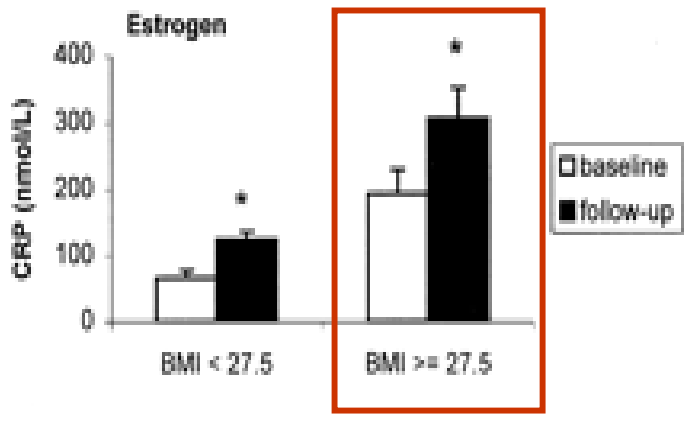
oral equine estrogens

increase IL-6 & CRP at *higher BMI*

systemic proinflammatory effect of estrogen
vs pro-vascular endothelial benefit by NO
which inhibits expression of cell adhesion molecules

[Herrington D et al JCEM 2001]





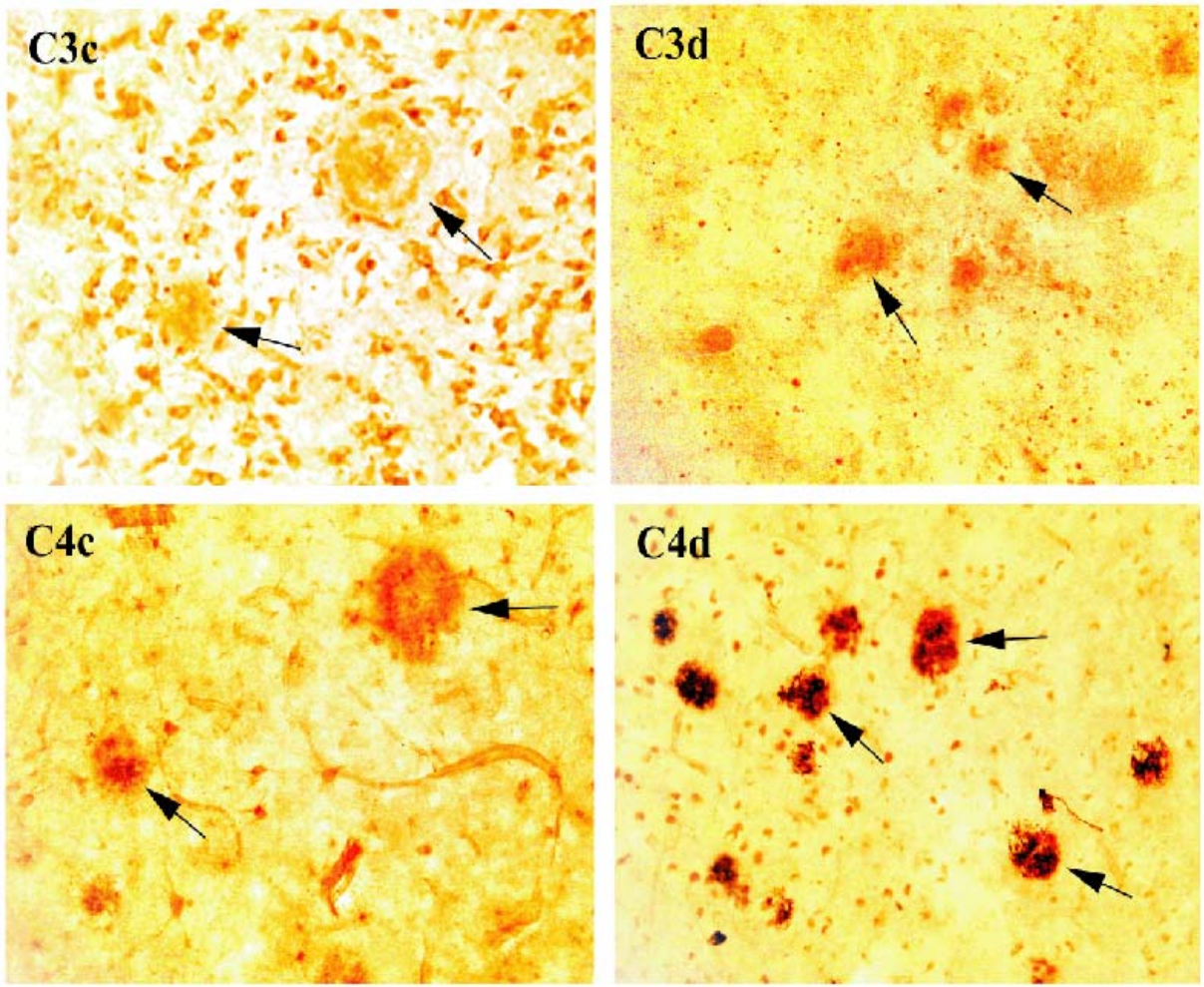
inflammatory markers in Alzheimer & usual brain aging

	senile plaque	aging human	aging rodent
glial activation: GFAP (astro), MhcII (µglia)	++	+	+
✂$_1$-ACT ✂$_2$-macroglobulin	+		
apoE , apoJ, CRP, HOX-1, RAGE	++	+	+
Complement C1q, C3	++	corpora amylacea	+ C1q mRNA
Cytokines IL-1, IL-6, TNF-✂	++	+	+

Complement activation in normal aging (CDR 0)

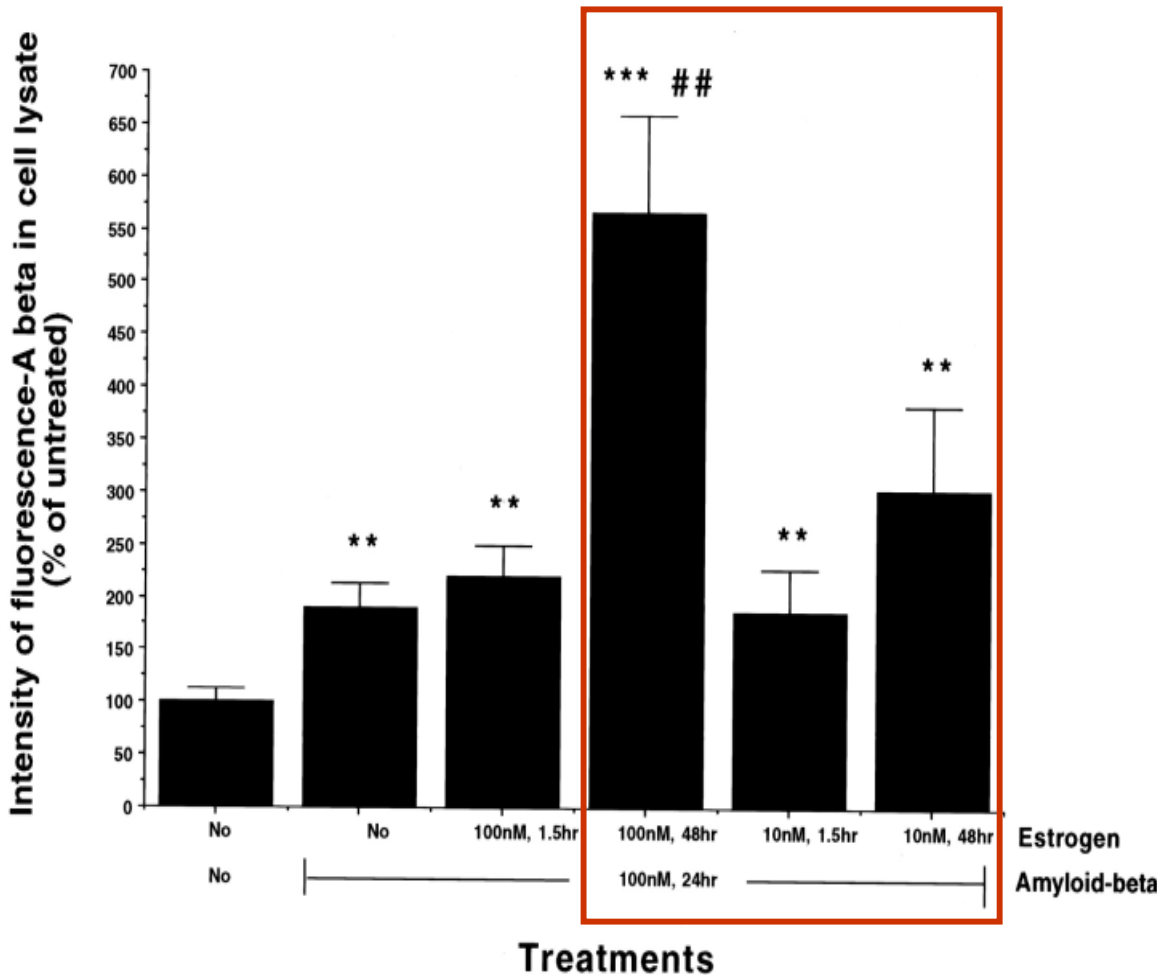
C3,C4 on diffuse Aβ deposits

H Zanjani, C Finch J Morris, J Price, ADRD, 2005

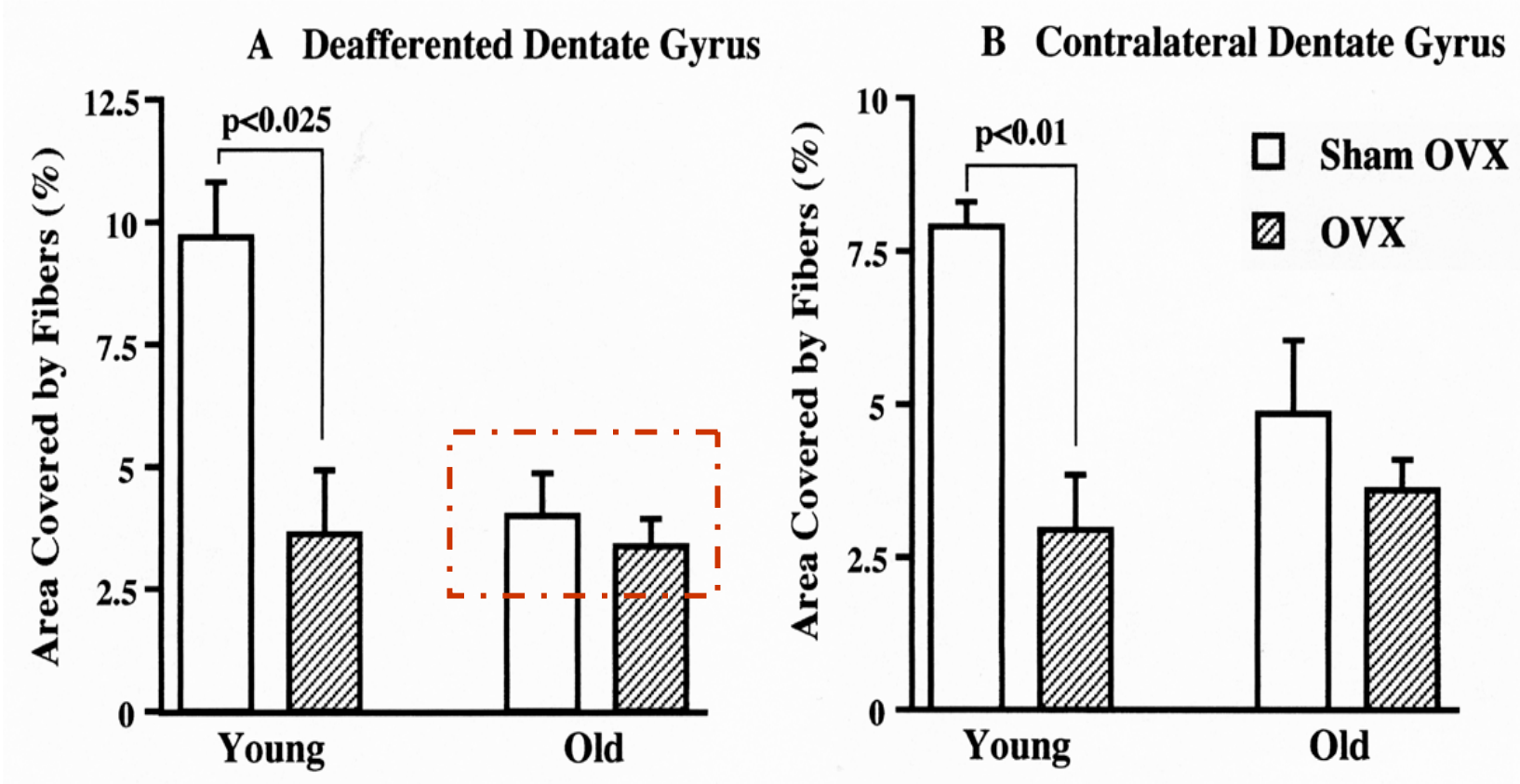


E2 increases microglial uptake of Abeta

Li et al., J Neurochem 2000

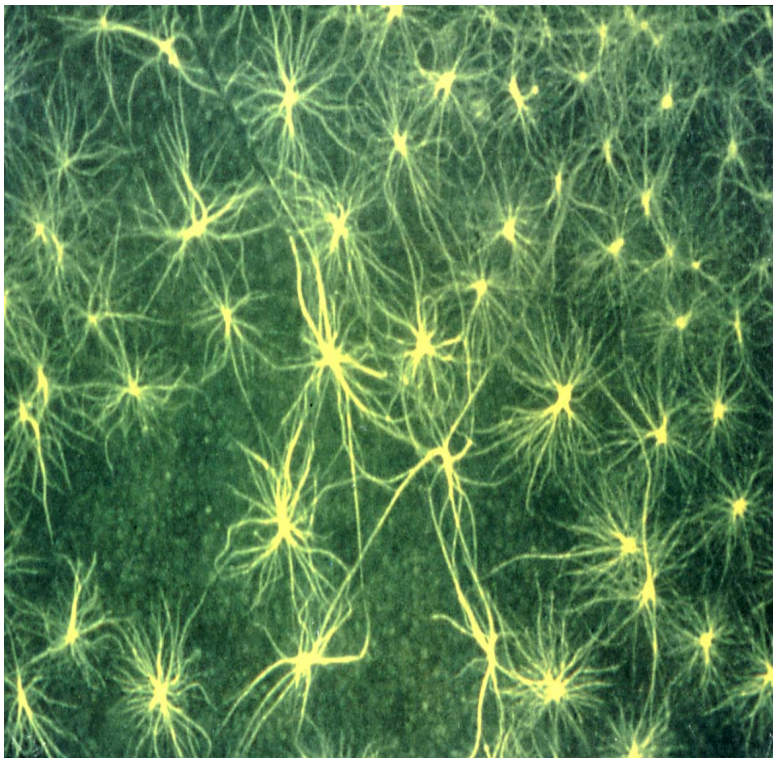


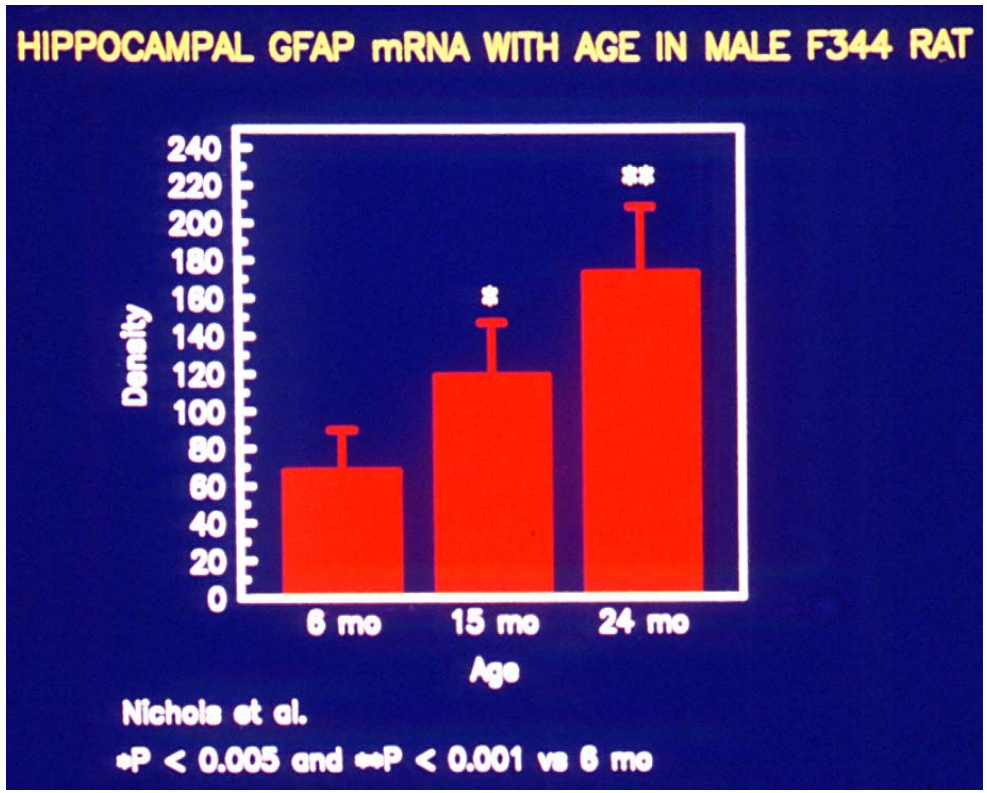
Aging decreases responsiveness of synaptic sprouting to E2



Stone, Rozovsky, Morgan, Finch (2000) *Exp Neurol*

Astrocyte aging increases GFAP-containing intermediate filaments





GFAP mRNA in normal aging rat brain

Nichols et al Neurobiol Aging 1995

aging astrocytes

(24 vs 3 mo)

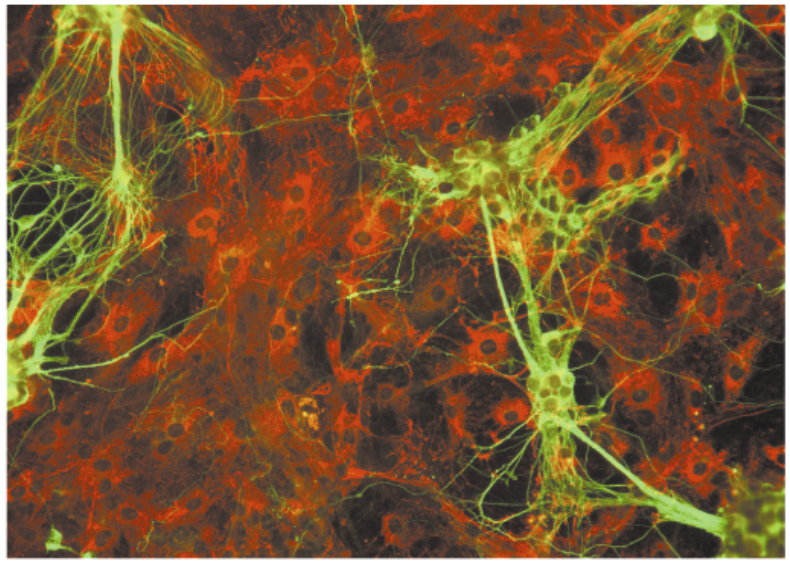
support less neurite growth

(E18 neurons)

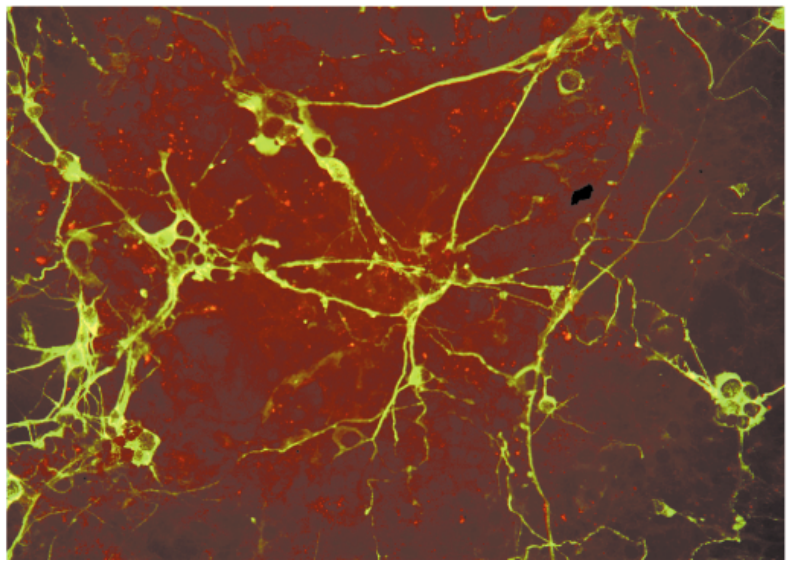
Rozovsky et al
Neurobiol Aging, 2005

Laminin/MAP-5 double immunolabeled astrocyte-neuron co-cultures

old glia



young glia

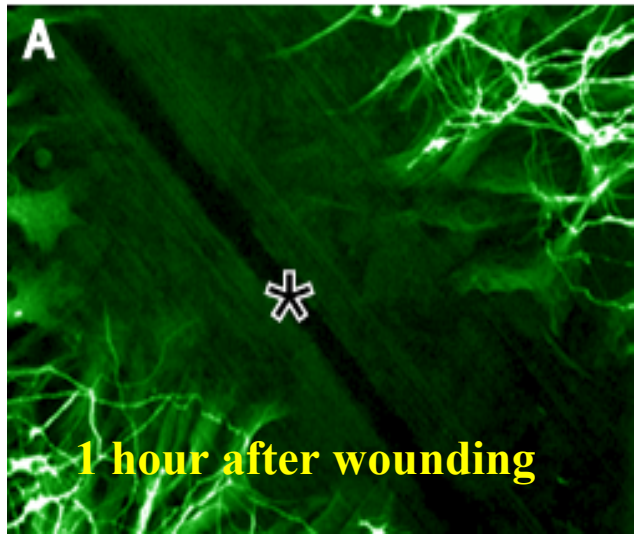


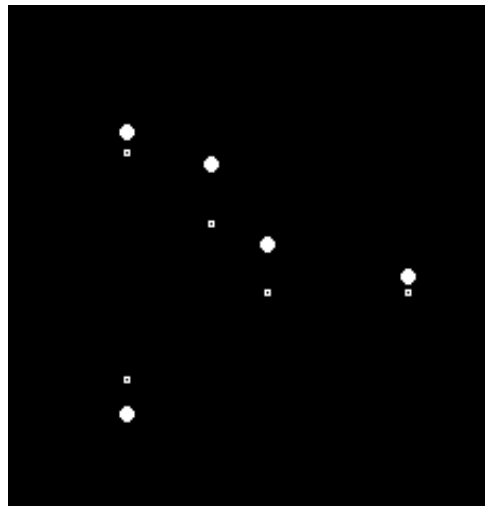
E2 enhances neurite outgrowth after wounding by GFAP repression

astrocyte: neuron cocultures

neonatal astrocytes; E18 neurons

Rozovsky Endocrinology 2002





Aging astrocytes

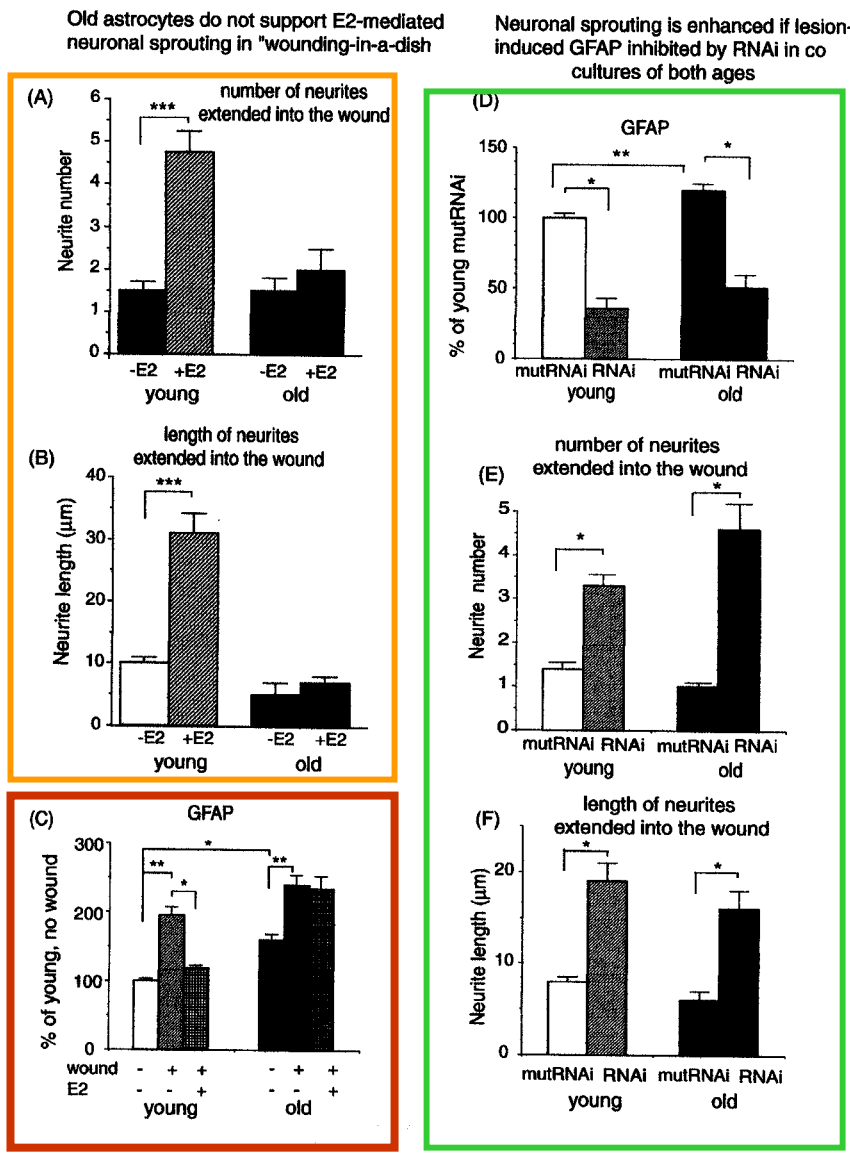
less responsive to E2

*neurite support

*GFAP repression

reversed by SiRNA to decrease GFAP

Rozovsky et al
Neurobiol Aging, in press



open questions
in neuroinflammatory processes of 'normal' brain aging and dementia

*effects of blood IL-6 and CRP etc on brain aging

*NSAIDs/aspirin/statins on brain aging

*estrogen-progestin interactions on brain aging

*apoE alleles and hormone therapy on brain aging