Animal Models of Neuroplasticity: or is it Cognitive Reserve?

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Student Definitions

- “Cognitive reserve is the concept used to describe patients who exhibit AD pathology without the associated cognitive defects.”
- “I will define brain cognitive reserve as functional compensation for AD pathology induced by enhancement of mental and physical activity.”

Overview:

- Impact of an enriched environment on building reserve in a higher animal model
- Role of BDNF in reserve – enables learning and recall
- Molecular reserve in MCI – reserve in action?

The aged canine as a model of human brain aging

- Canines develop learning and memory deficits beginning in middle age.
- Like humans, with age, canines:
  - show increased individual variability in cognition.
  - naturally accumulate beta-amyloid.
  - Accumulate oxidative damage (proteins, lipids) and mitochondrial dysfunction
- Represents an animal model of MCI

Can Behavioral Enrichment/Exercise, and/or Diet, reduce the Development of Age-Dependent Cognitive Dysfunction in Canines?

Longitudinal Study

	Aox Diet (-)	**Aox Diet (+)**
Behavioral Enrichment (-)	N=12 Old	N=12 Old
Behavioral Enrichment (+)	N=12 Old N=8 Young	N=12 Old N=9 Young

Old beagles – 8 to 12 years at start
Young beagles – 2 to 5 years at start
Treatment duration – 2.8 years

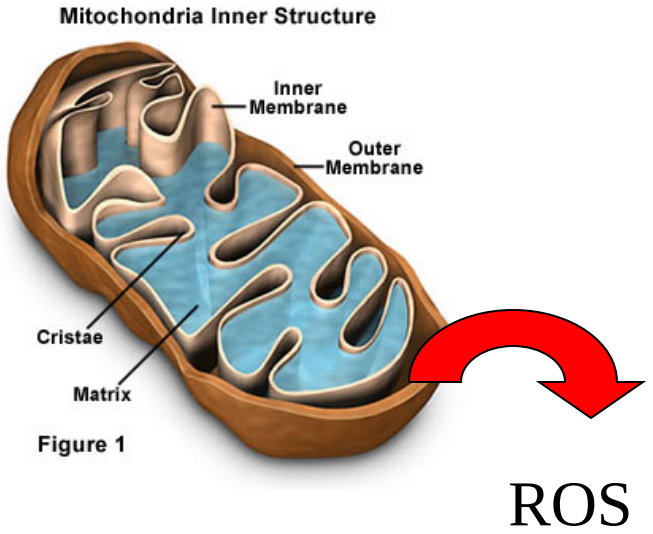
Canine Antioxidant Diet

Antioxidants

- dl-alpha tocopherol acetate-1050 ppm (20 mg/kg - 800 IU/day)
- Stay-C (ascorbyl monophosphate)-100 ppm or ~100 mg/day
- Spinach, carrot granules, tomato pomace, citrus pulp, grape pomace: 1% each in exchange for corn (Increased ORAC by 50%, equivalent to 4-5 servings of fruits and vegetables/day)

Mitochondrial cofactors

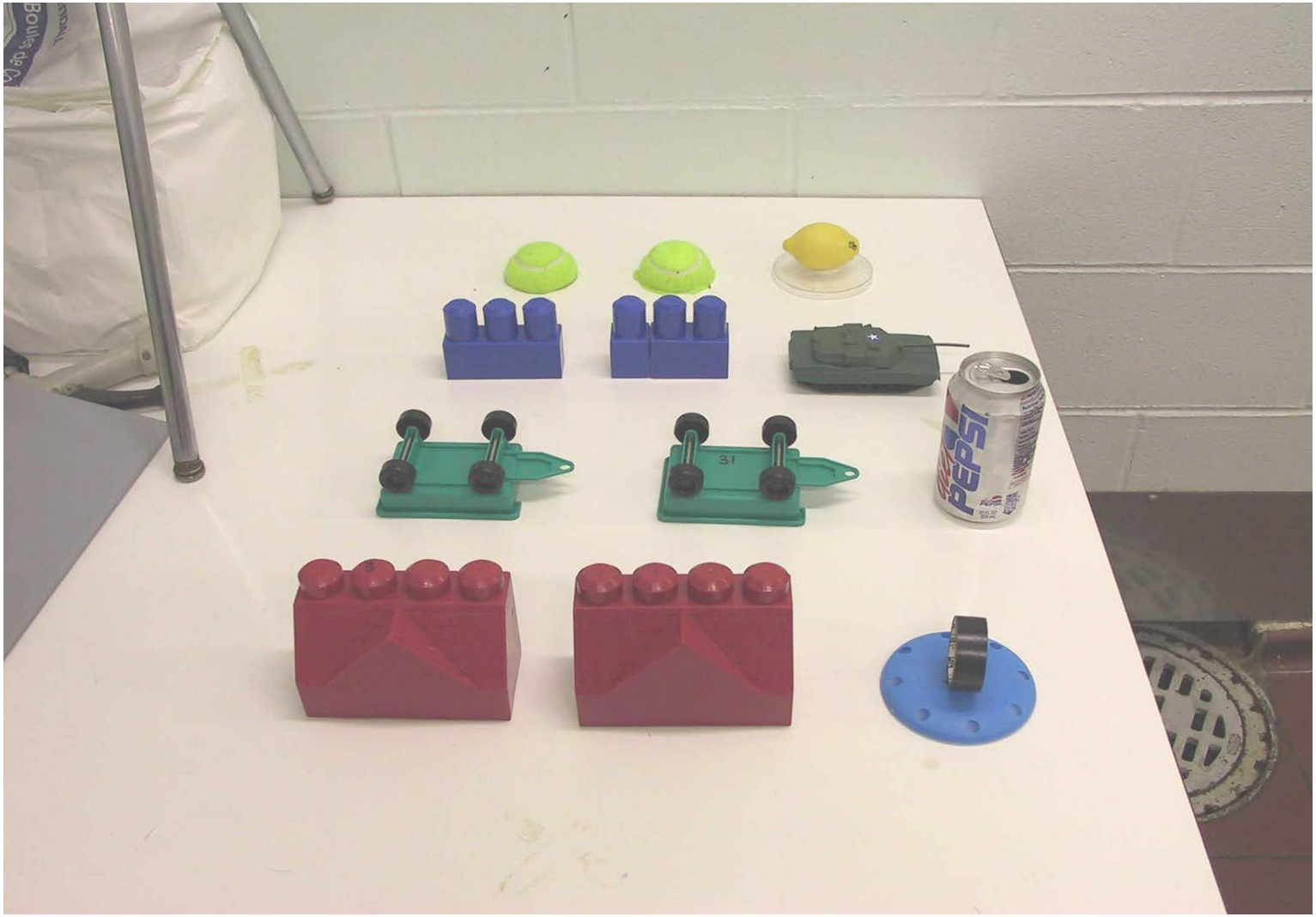
- dl-Lipoic acid: 135 ppm (2.7 mg/kg)
- l-carnitine: 300 ppm (6 mg/kg)



Enrichment Protocol

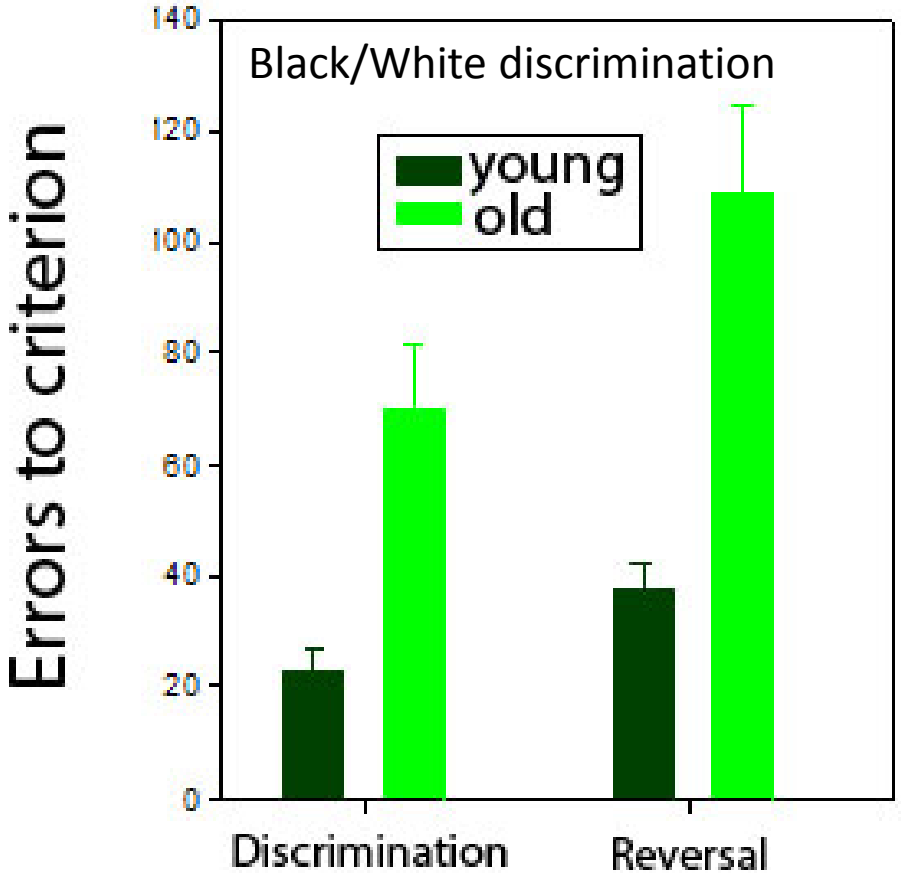
- Play toys
- Kennelmate
- 3-4 weekly walks
- Additional cognitive experience/education

Controls



Discrimination learning: shape, color, size

Discrimination Learning is impaired with age

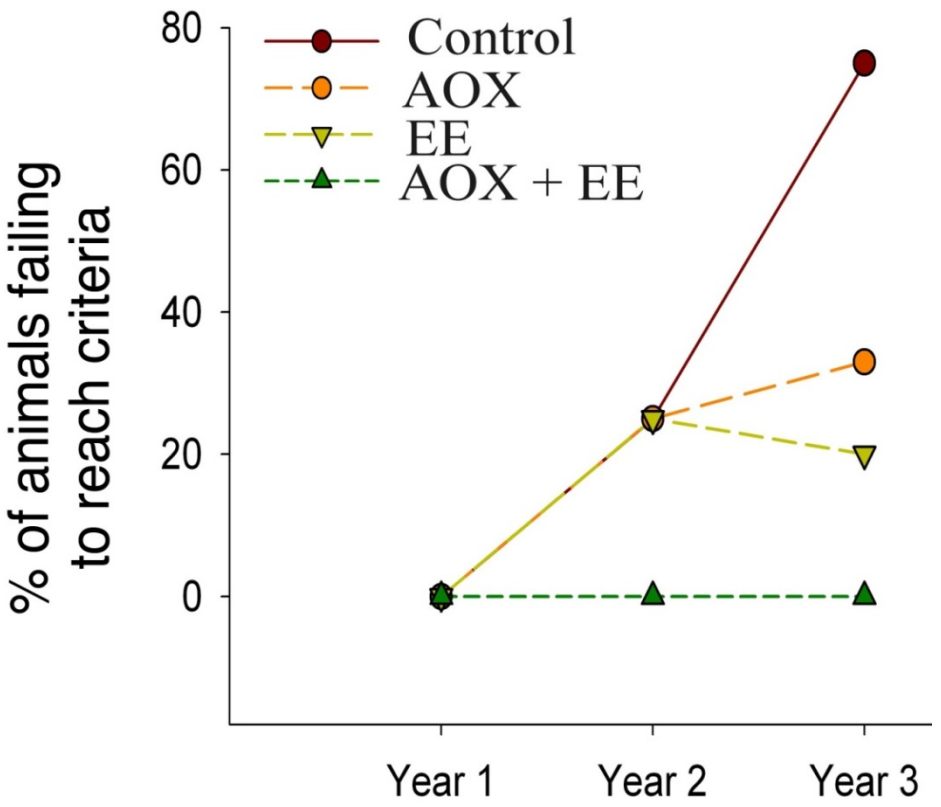


- 10 trials/day
- 40 training sessions
- Criteria: 70% of trials correct, 3 successive test sessions

Combined intervention (EE+AOX) prevents cognitive decline with age

EE = behavioral enrichment
AOX = antioxidant diet

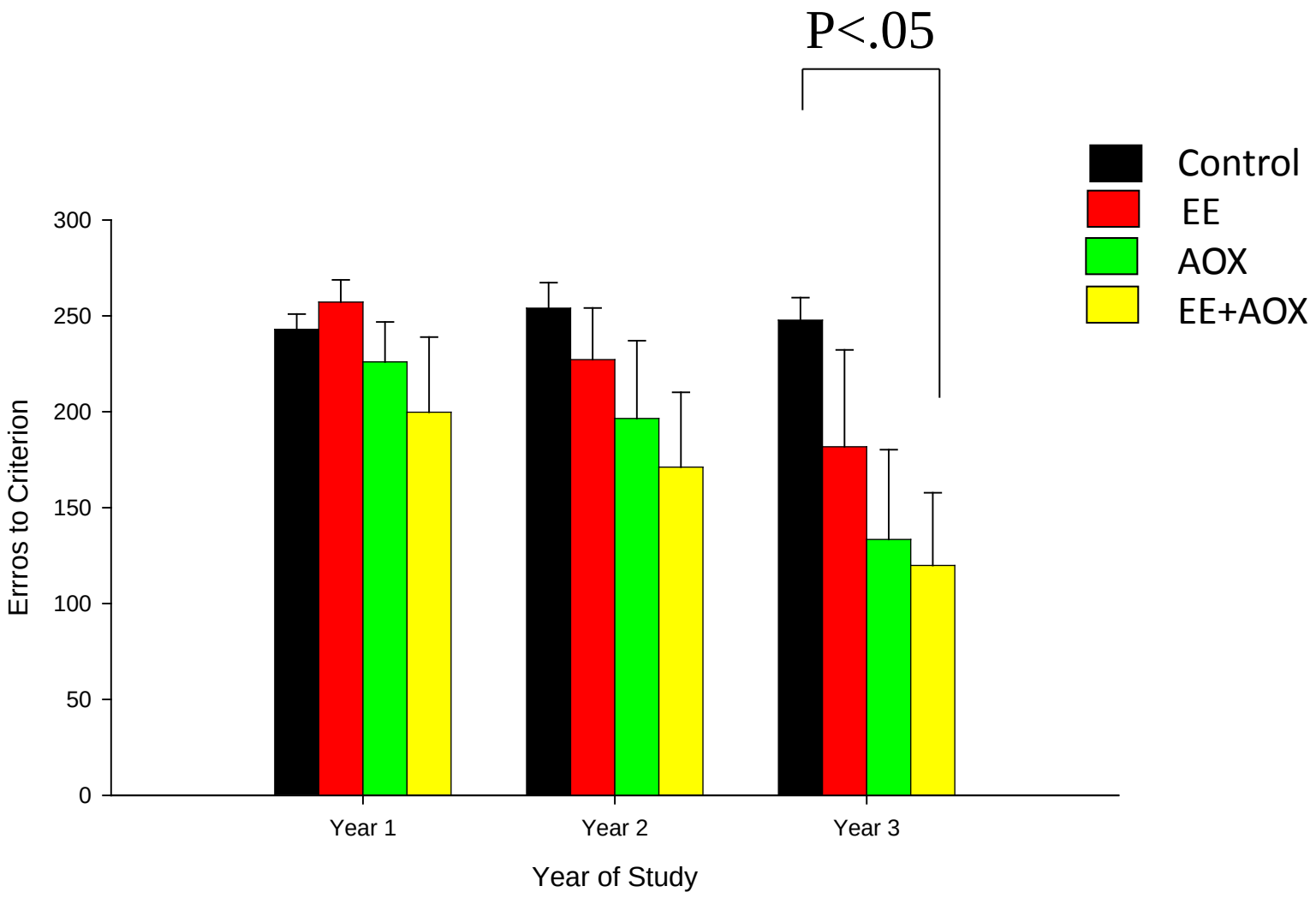
Reversal performance:



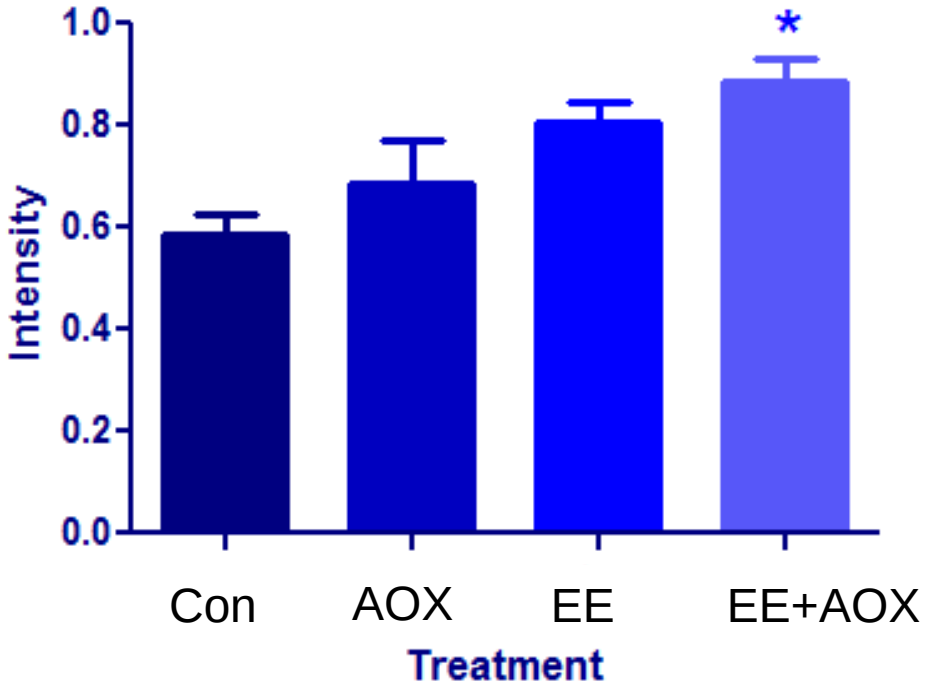
Task:	Object	Size	B/W discrim

Can the interventions "reverse" age-related cognitive dysfunction?

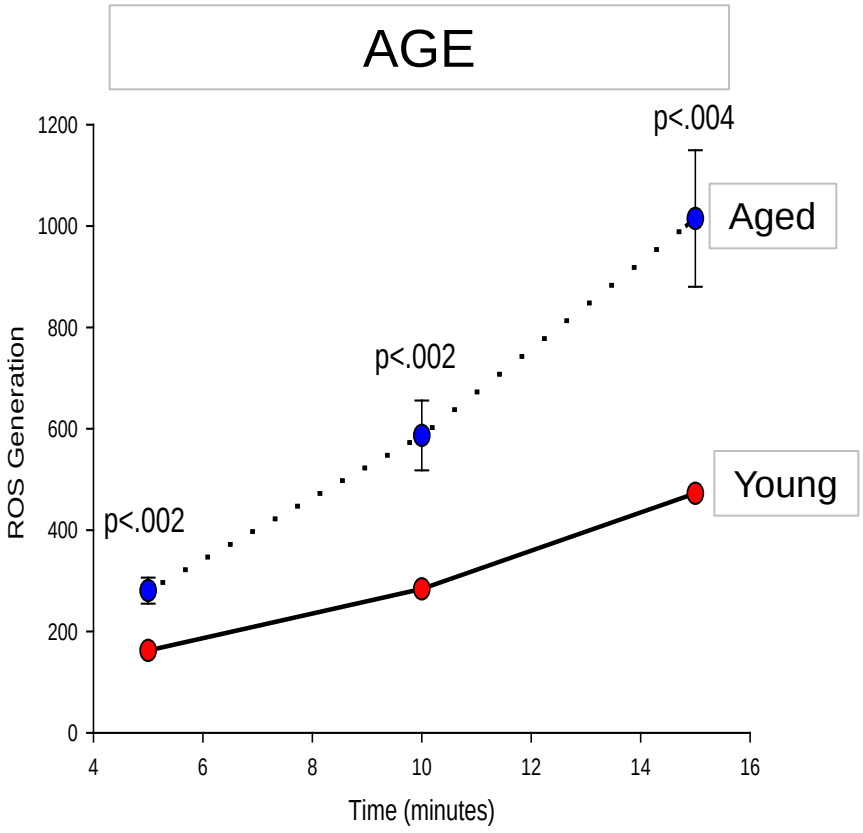
Spatial Memory improved by EE+AOX

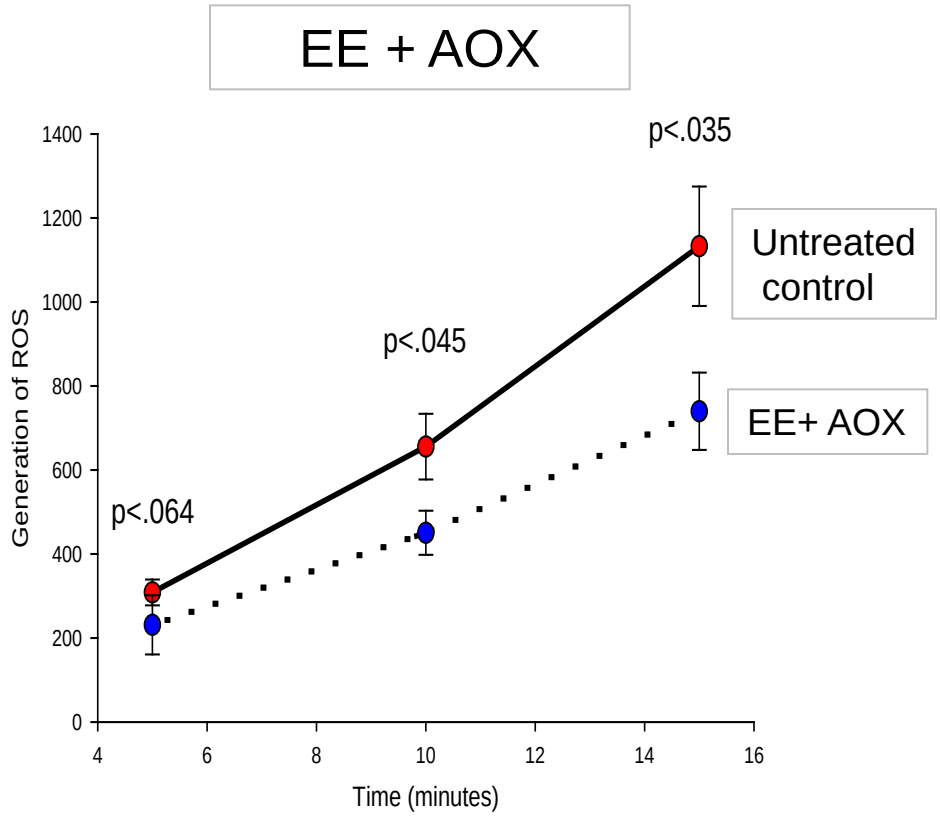


Synapse Markers are increased in the combined treatment group (SNAP25)



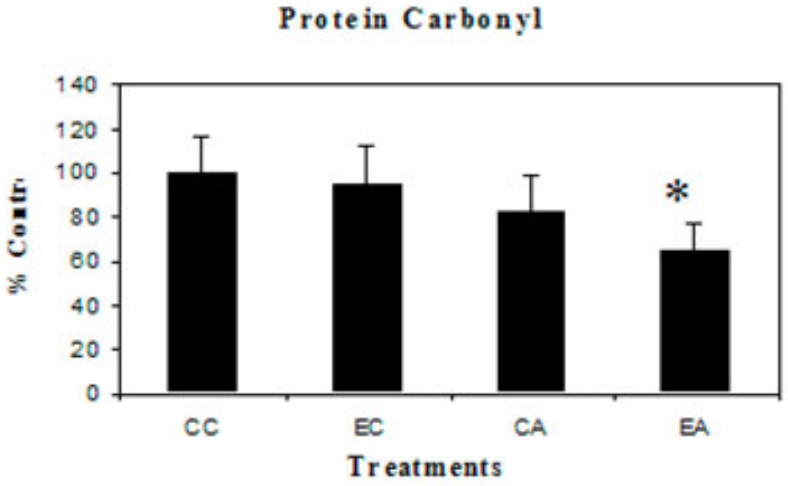
Mitochondrial ROS production as a function of age and EE+AOX treatment

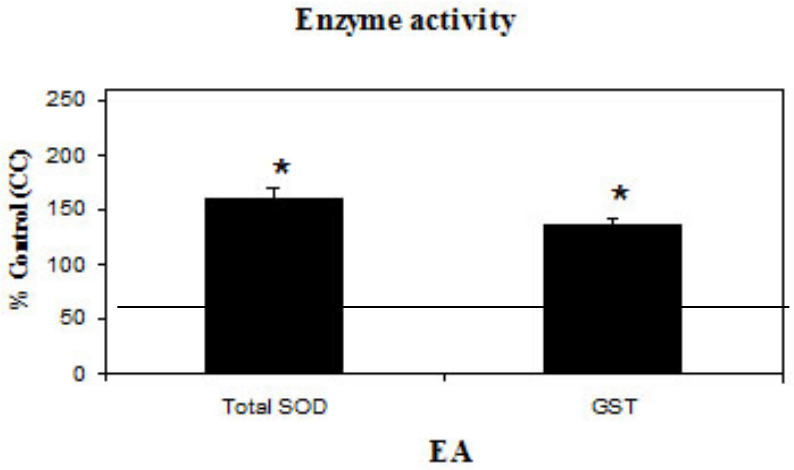


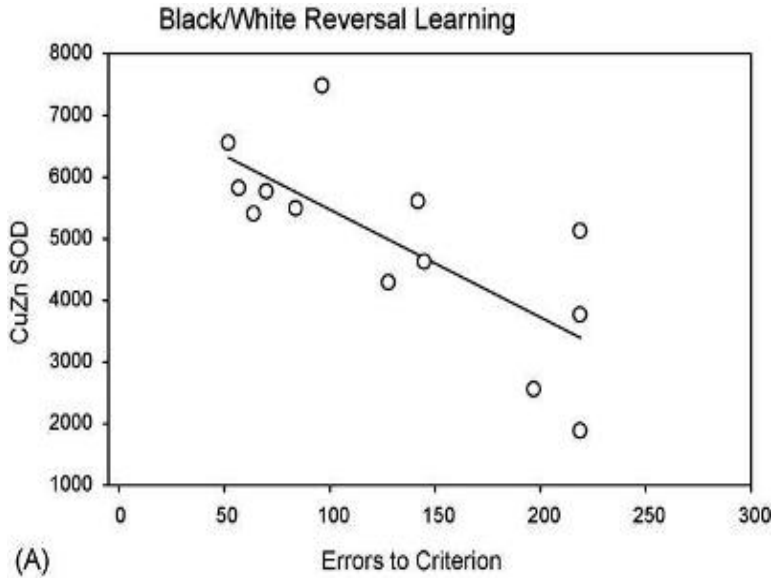


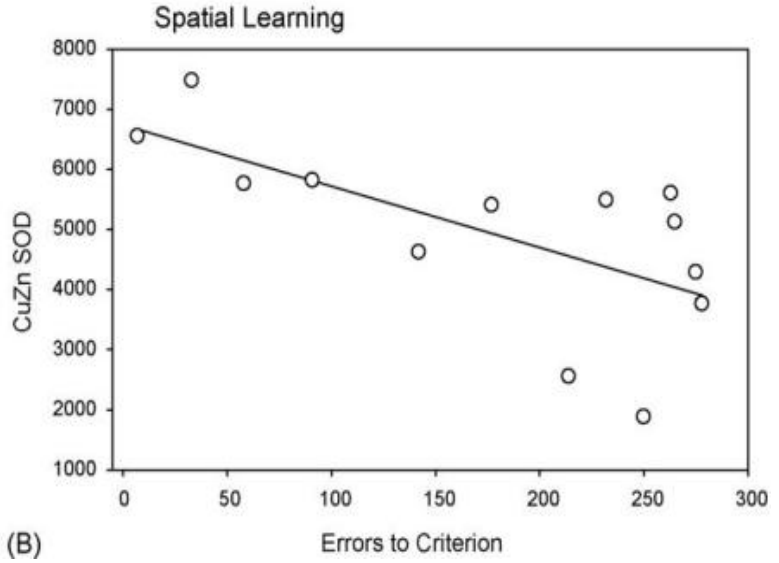
Head, Cotman, Sullivan, 2009

Enrichment+AOX reduces age-related oxidative damage: SOD, superoxide to water; GST, detoxifies HNE





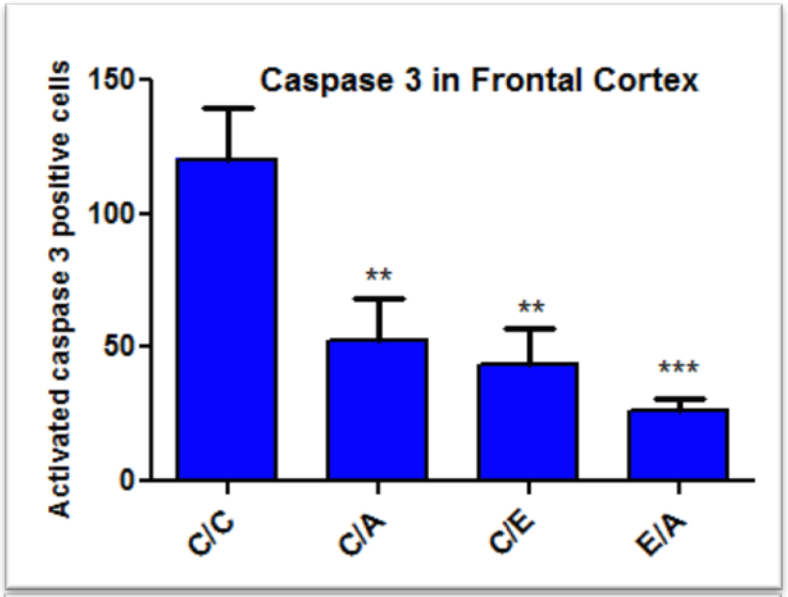


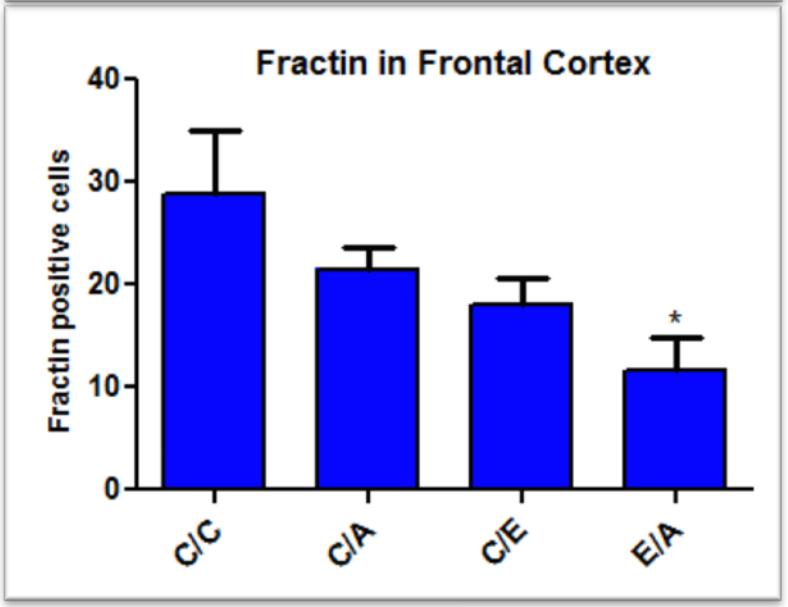


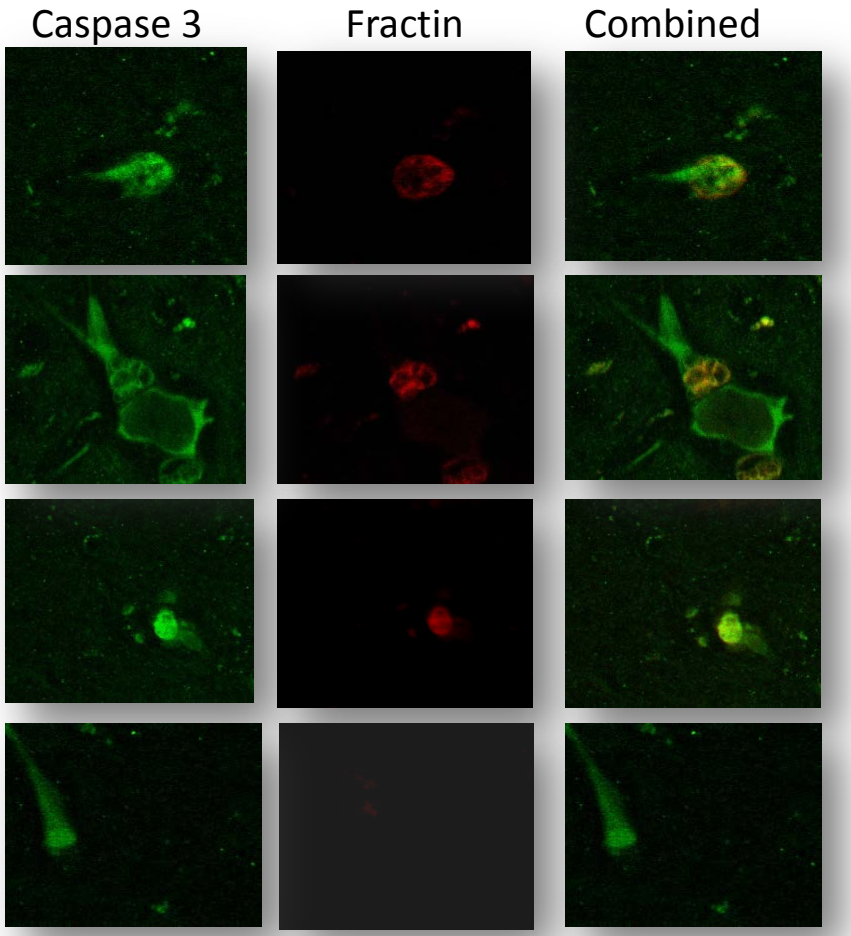
(Oppi, Cotman, et al., 2008)

The Interventions reduce age-related Caspase-3 activation

Control (C/C), antioxidant (C/A) , enrichment (C/E) combination (E/A)

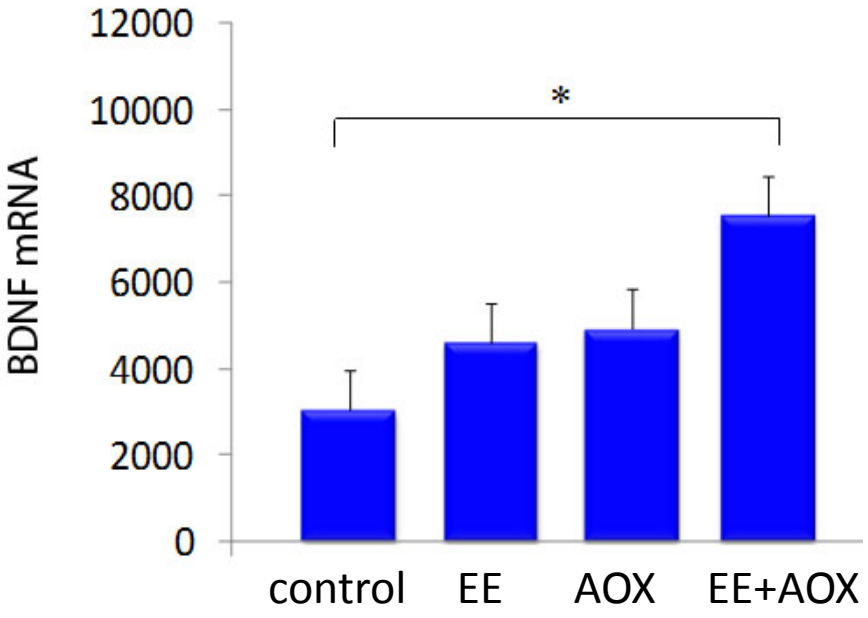


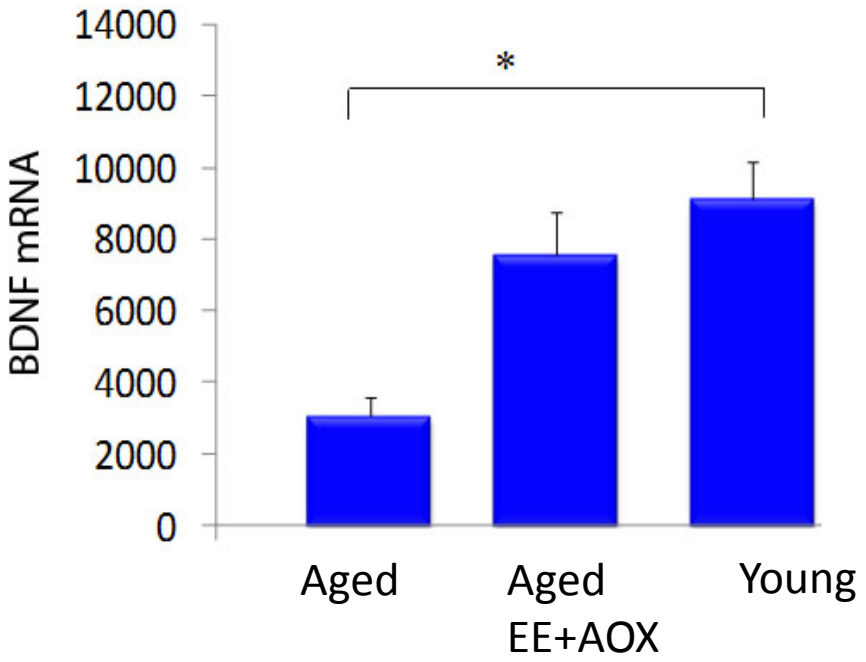




Immunofluorescent staining for cleaved caspase-3 and cleaved product (fractin) in the canine frontal cortex.

Combined EE+AOX increases BDNF mRNA, and counteracts BDNF decline with age



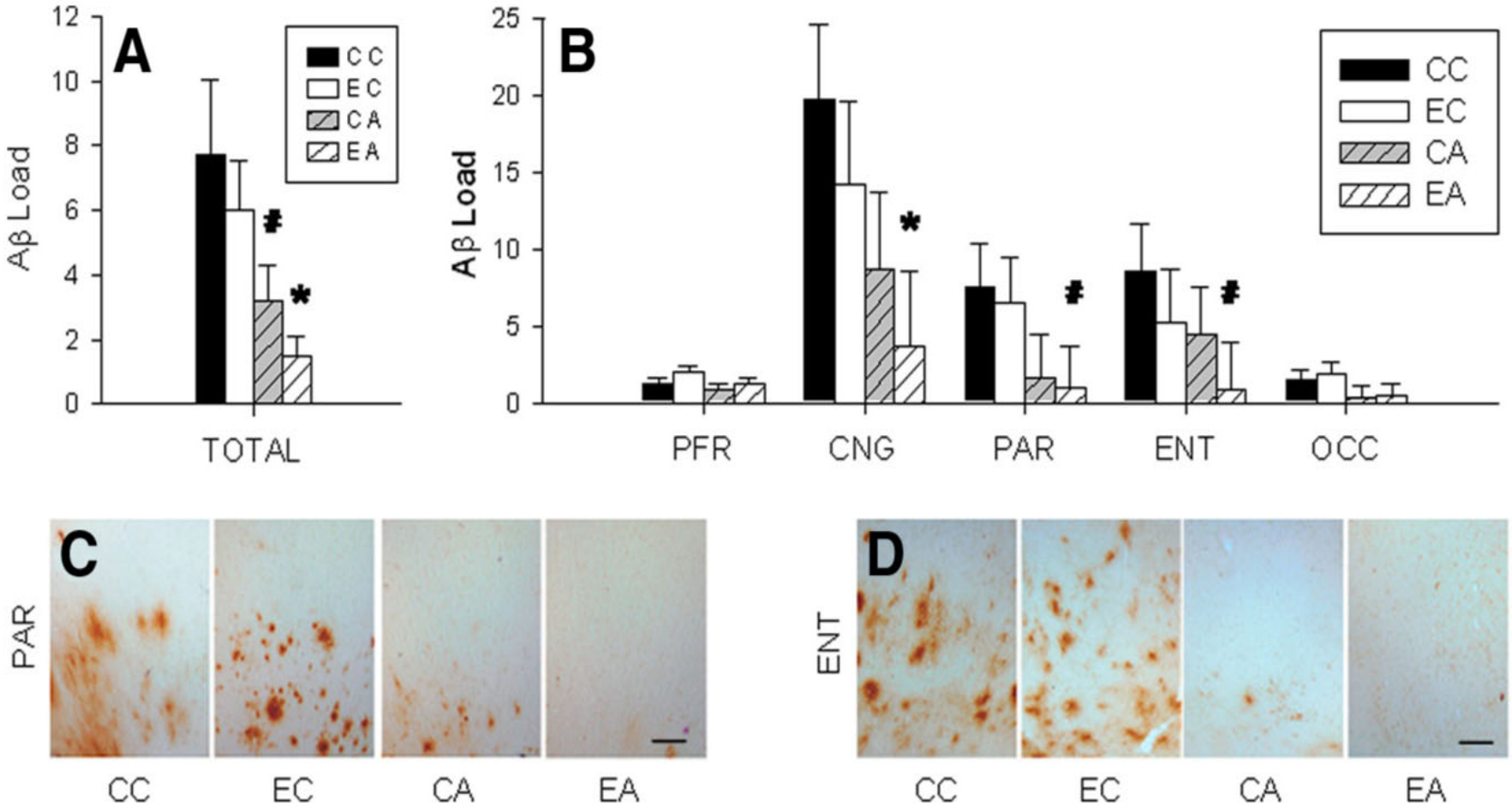


(Fahnestock, Cotman, et al., 2010)

How do the treatments affect Beta-amyloid?

- Levels decreased?
- Or maybe increased tolerance?

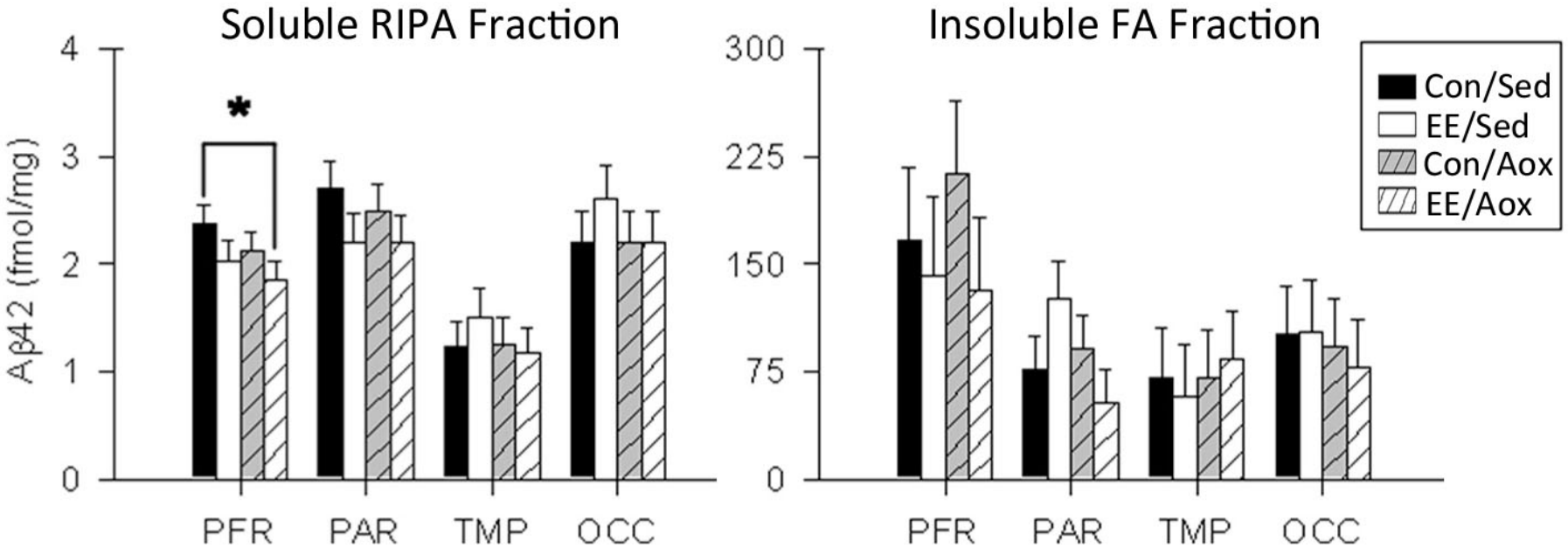
Combined EE+AOX decreases beta-amyloid plaque load.



Change in Amyloid load does not correlate with behavioral improvement

	Pearson correlation	p value
Spatial Memory Performance	0.198	n.s
Black/white discrimination errors	-0.096	n.s
Black/white reversal errors	-0.134	n.s

Enrichment, Aox treatment: minimally reduce AB42



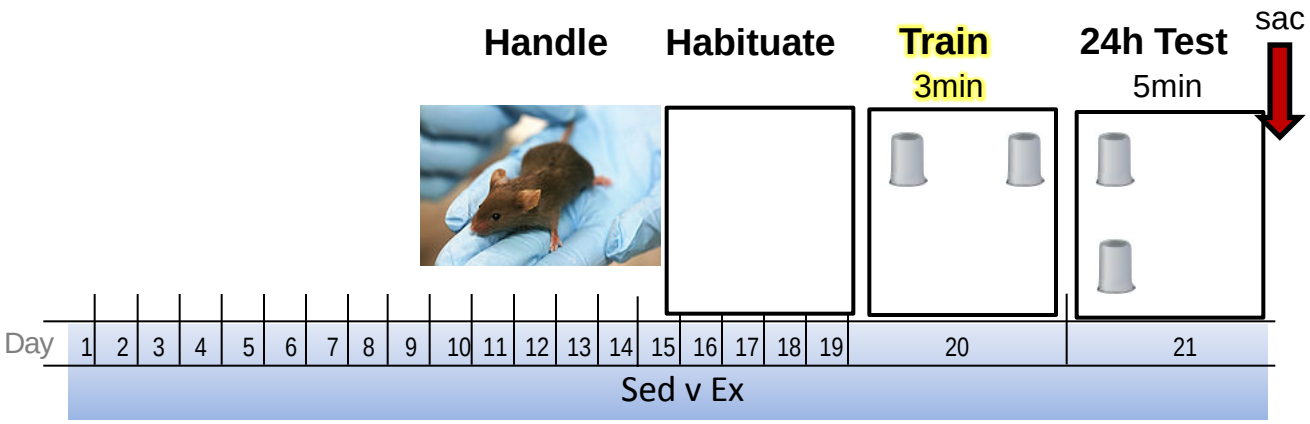
Hypothesis for synergistic effectiveness of the combined EE + AOX treatment

- AOX intervention improves mitochondrial function:
  - may **"enable"** enrichment stimuli to better engage plasticity and protective mechanisms
- Combined EE+AOX results in greater learning improvements, pathology reduction, and BDNF induction than either EE or AOX alone
- Brain tolerates β-amyloid

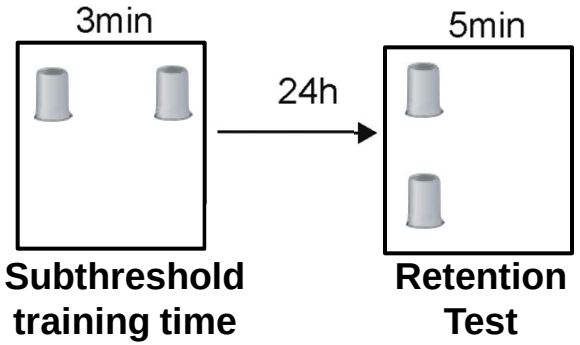
Role of BDNF/Exercise on Enabling Cognitive Performance

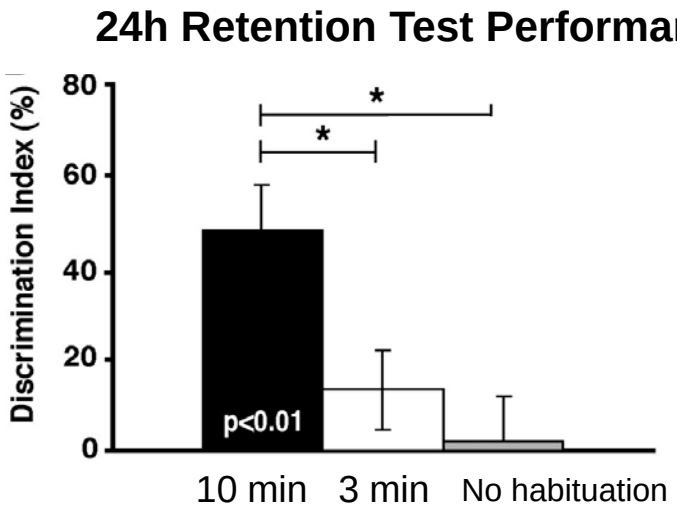
- Can BDNF/exercise enable learning of normally sub-threshold events?
  - Test with Object Location Memory Task, an example of hippocampal-dependent “incidental” learning
- How critical is exercise-induction of BDNF in hippocampus for enabling learning?

Exercise mice 3 wks, expose to sub-threshold training for object location memory and determine if mice now learn and retain experience 24hrs



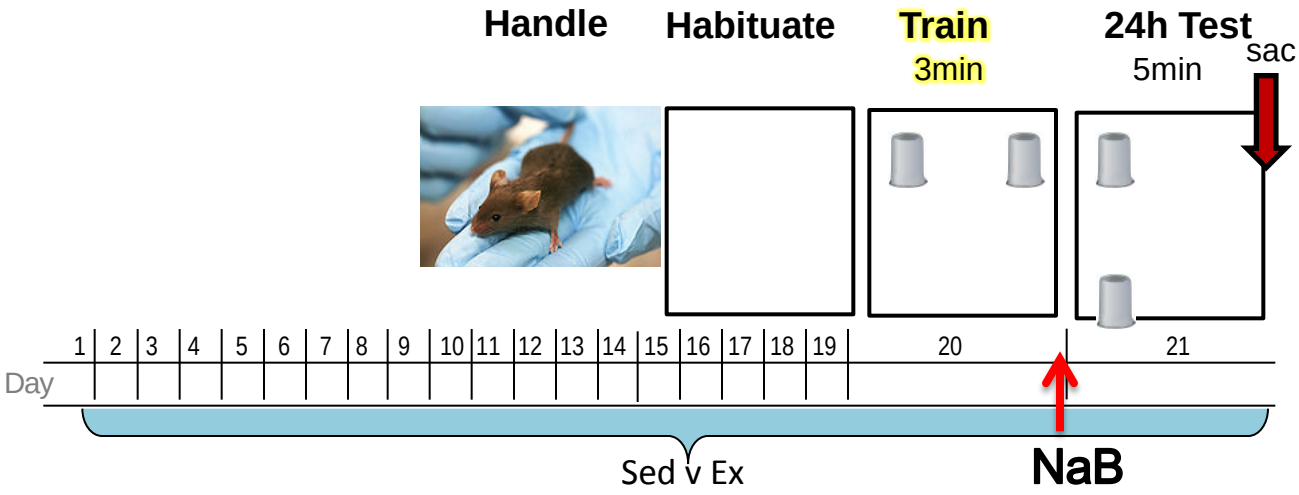
Sub-threshold training (3 min): animal cannot discriminate between familiar and novel object location



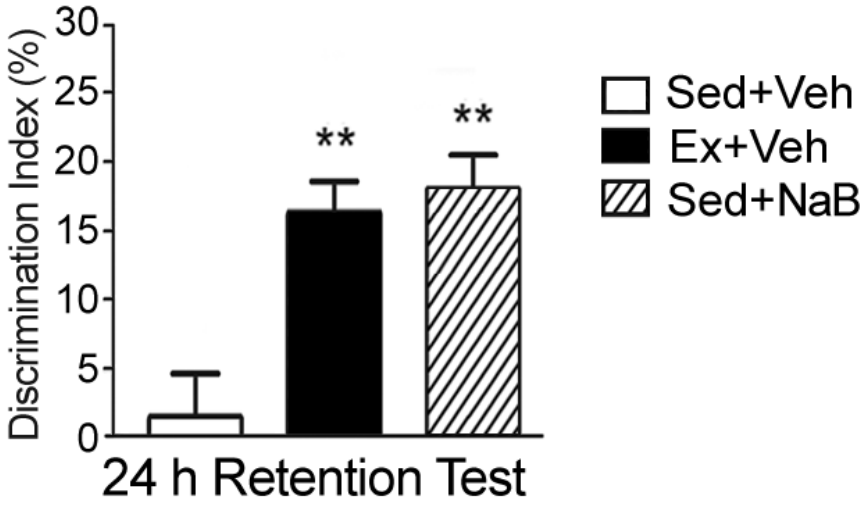


(Stefanko et al. 2009)

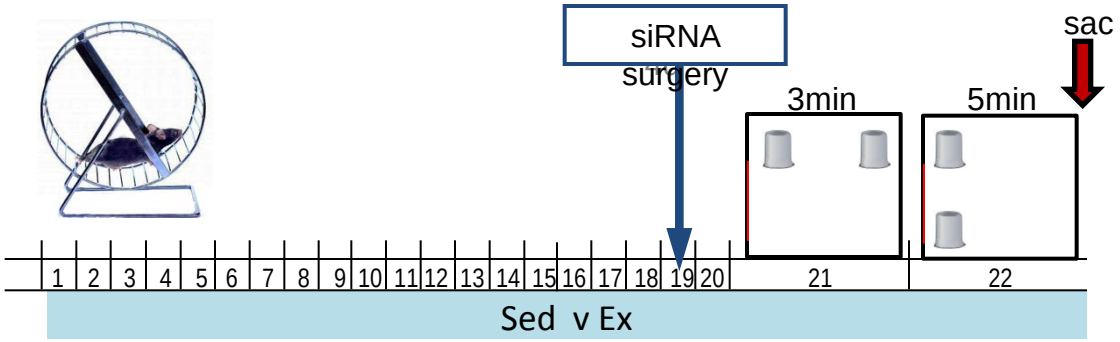
Exercise enables sub-threshold learning
The effectis equivalent to Sodium Butyrate (NaB) – a histone deacetylase inhibitor

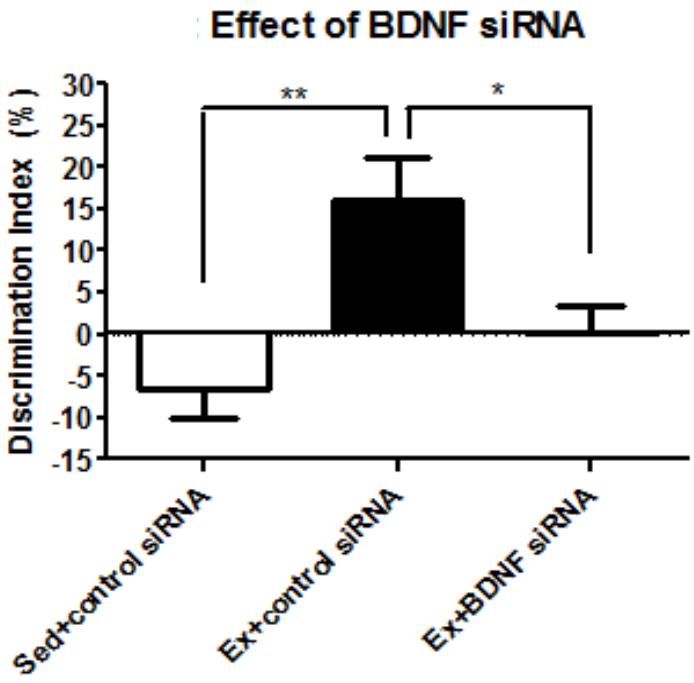


<u>Sub-threshold OLM performance</u>
(long term memory)



BDNF is required for Exercise to enable sub-threshold learning





Blocking exercise induction of BDNF with siRNA prevents discrimination of the novel location

Does MCI engage Molecular Reserve ?

- Is MCI mild AD?
- Are compensatory molecular mechanisms engaged in the MCI brain?
- Evaluate with microarray analyses

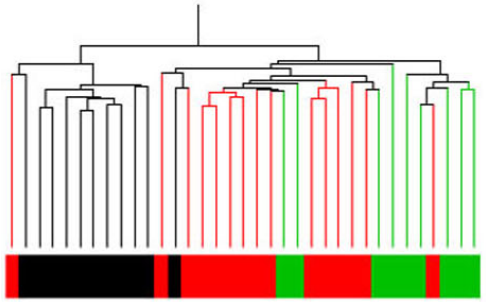
Microarray study: MCI, AD, normal aged

- Well powered microarray study (63 cases, see below)
- 4 brain regions
  - EC, HC, Superior Frontal Gyrus (SFG)
  - Somatosensory gyrus (PCG) – "control region"
- Affymetrix (HgU133 plus 2.0 chips)

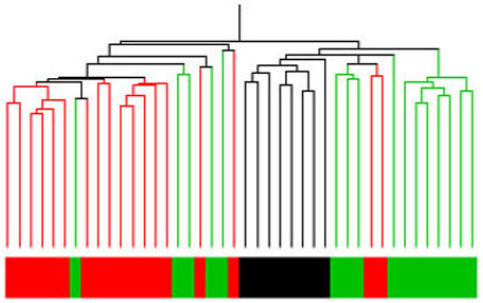
	cases	age (yrs)	brain regions	# arrays
Aged Control	24	85 ± 6.8	EC, HC, SFG, PCG	57
MCI	12	87 ± 4.4	EC, HC, SFG, PCG	40
AD	27	85 ± 6.2	EC, HC, SFG, PCG	78

MCI cases cluster closely

Entorhinal Cx

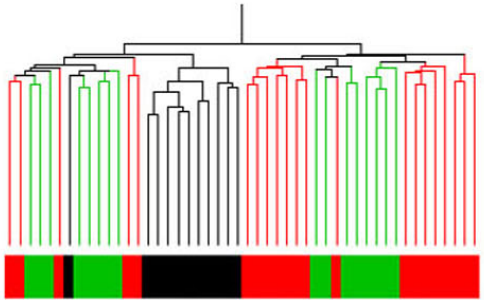


Hippocampus

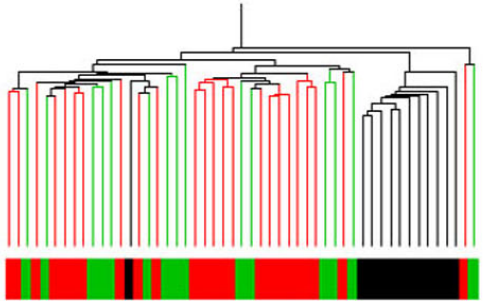


Black: MCI
Red: AD
Green: Aged Control

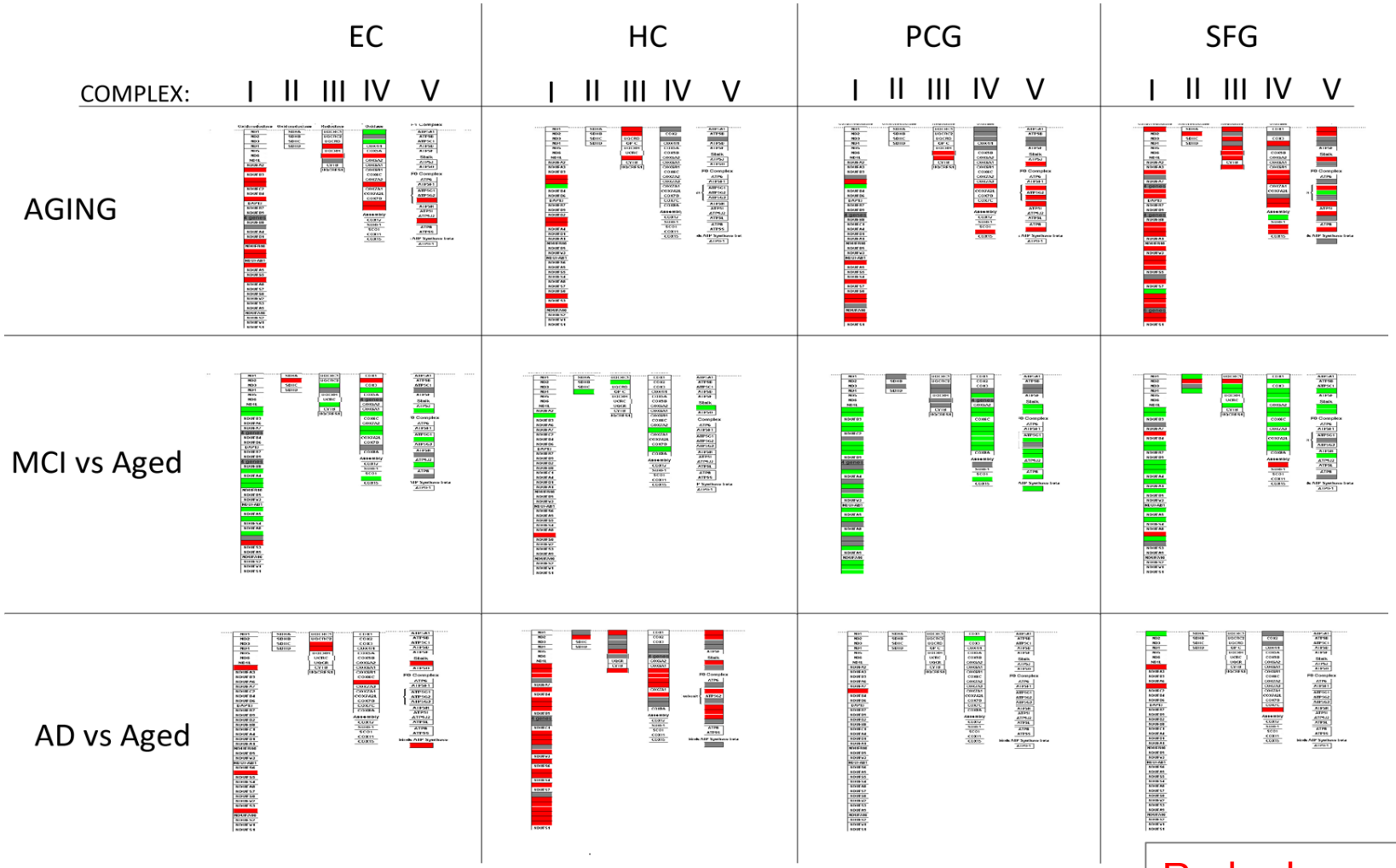
Prefrontal Cx



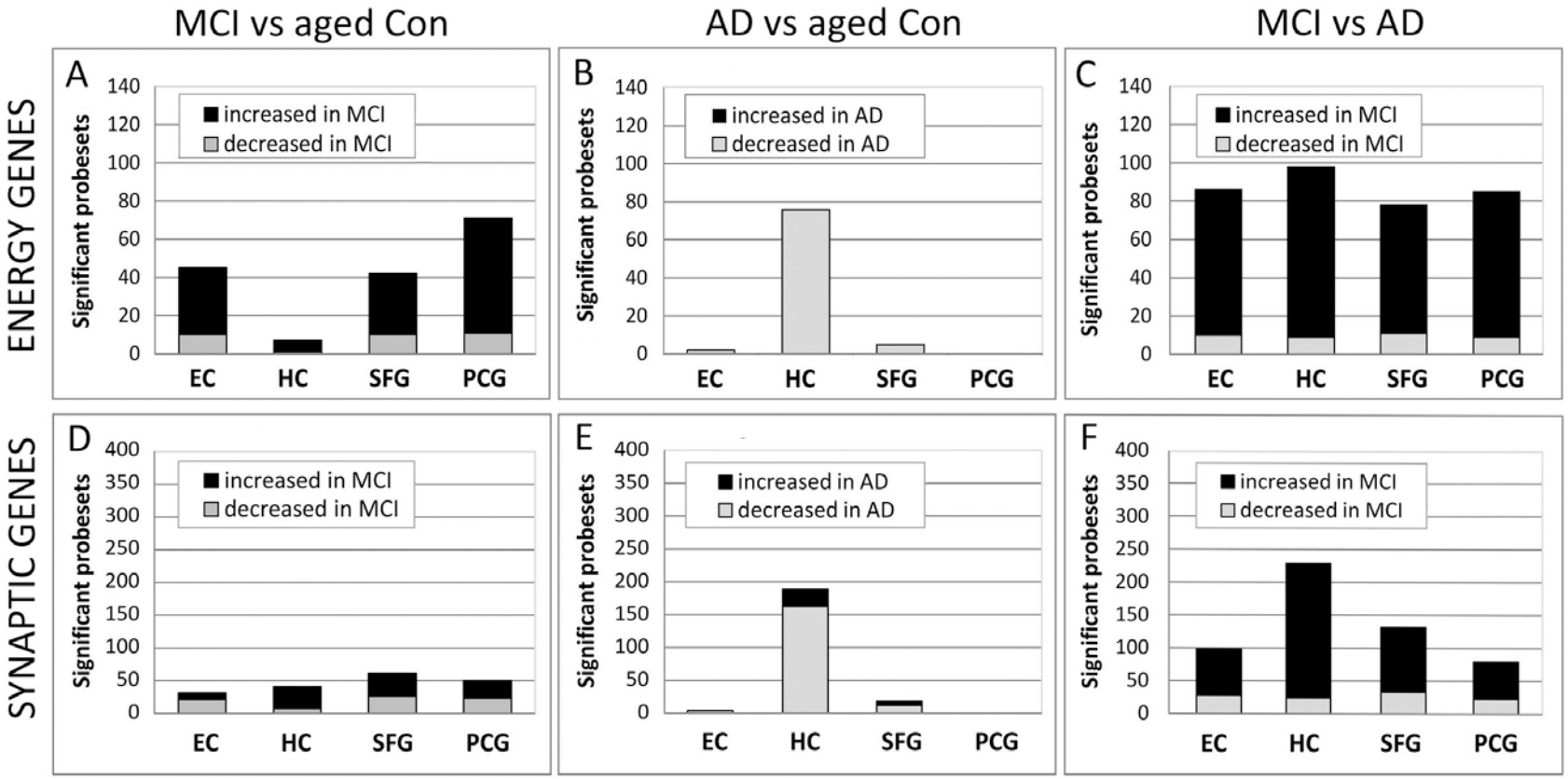
Somatosensory Cx



Electron transport genes: extensive upregulation across brain in MCI



Energy and synaptic genes: Downregulated in AD, but Upregulated in MCI



MCI brain mobilizes mechanisms to increase anabolic + metabolic function

- Upregulation of Protein biosynthesis/trafficking/ turnover
- Synaptic genes mobilized
  - Neurotransmitter release machinery (SNAREs)
  - Neurotransmitter receptors (Glu, GABA, Ach)
  - Synaptic structure and stabilization genes
- Upregulation of Mitochondrial energy generation
- **Molecular mobilization in MCI brain, likely serving to support cognitive reserve (ultimately fails with decline to AD)**

Summary

- Brain mobilizes many diverse mechanisms to maintain function in the wake of age and pathology build up.
- Environmental enrichment, exercise, and cognitive training enhance molecular counteractive strategies
- Even in MCI the molecular machinery is engaged to counteract decline
- Cognitive reserve may be integrated brain plasticity

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MCI: Gene expression is not intermediate between Aged and AD profiles