Exercise induces BDNF, improves learning and reduces β-amyloid

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Behavioral Interventions: The New Direction

Exercise

Mental Activity

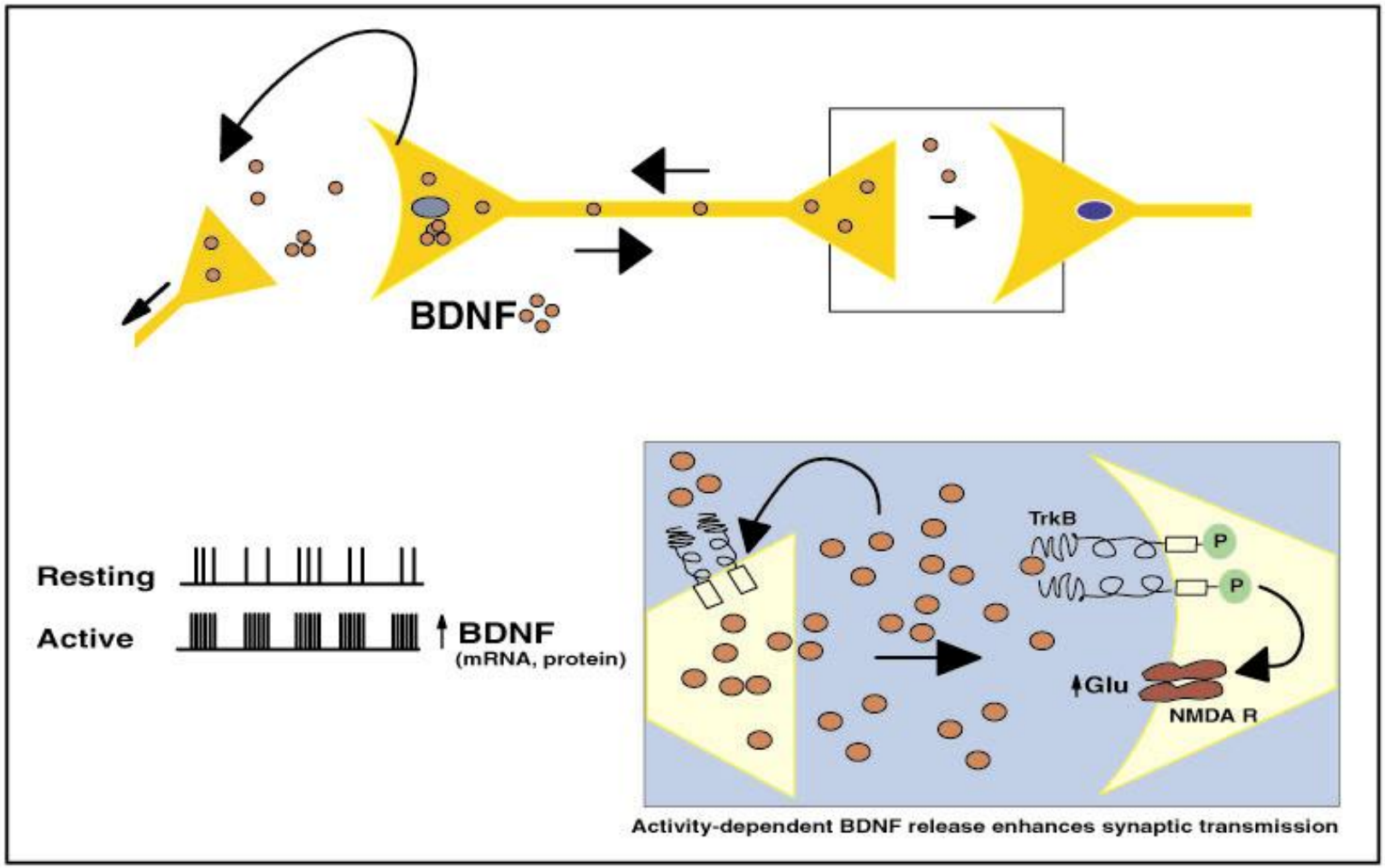
Diet

Outline

Part 1. Can exercise induce neurotrophic factors and improve learning?

Part 2. Can exercise reduce pathology in a AD transgenic mouse and improve learning?

BDNF (Brain Derived Neurotrophic Factor) is a Synaptic Modulator:



BDNF – Brain Derived Neurotrophic Factor

- Necessary for learning and long term synaptic change
- Stimulates synaptic growth and neurogenesis
- Protects neurons from injury

How to get more?

- Simple - exercise

Is BDNF increased by exercise in the brain ?

- Where? And how fast and long lasting?
- How much exercise?

Exercise increases BDNF mRNA

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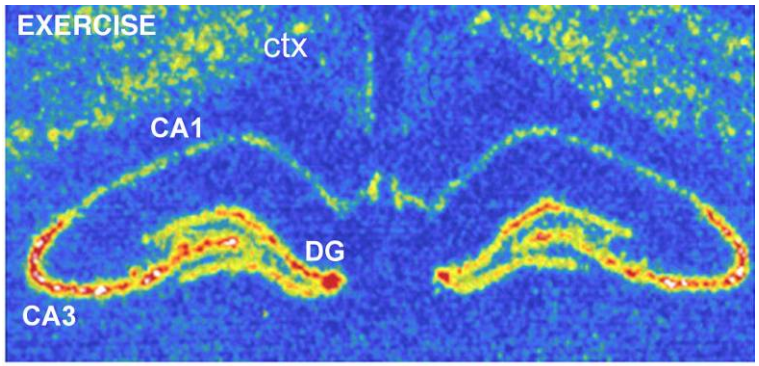
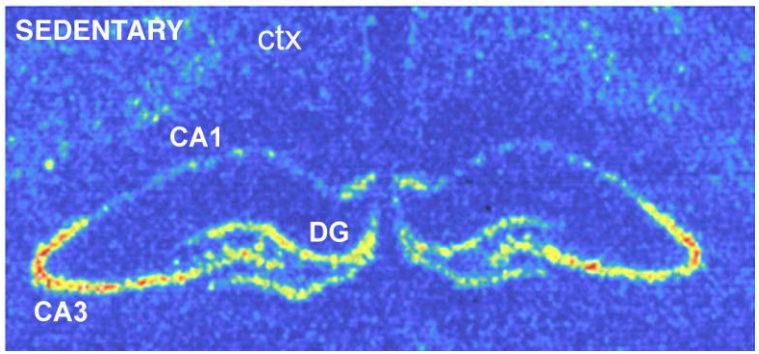
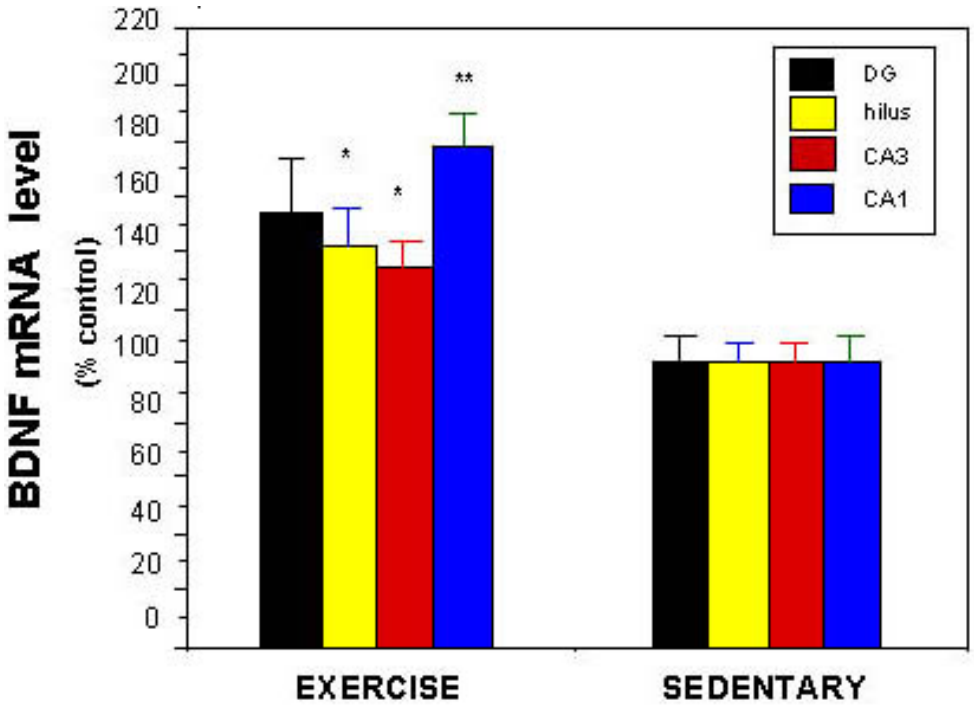


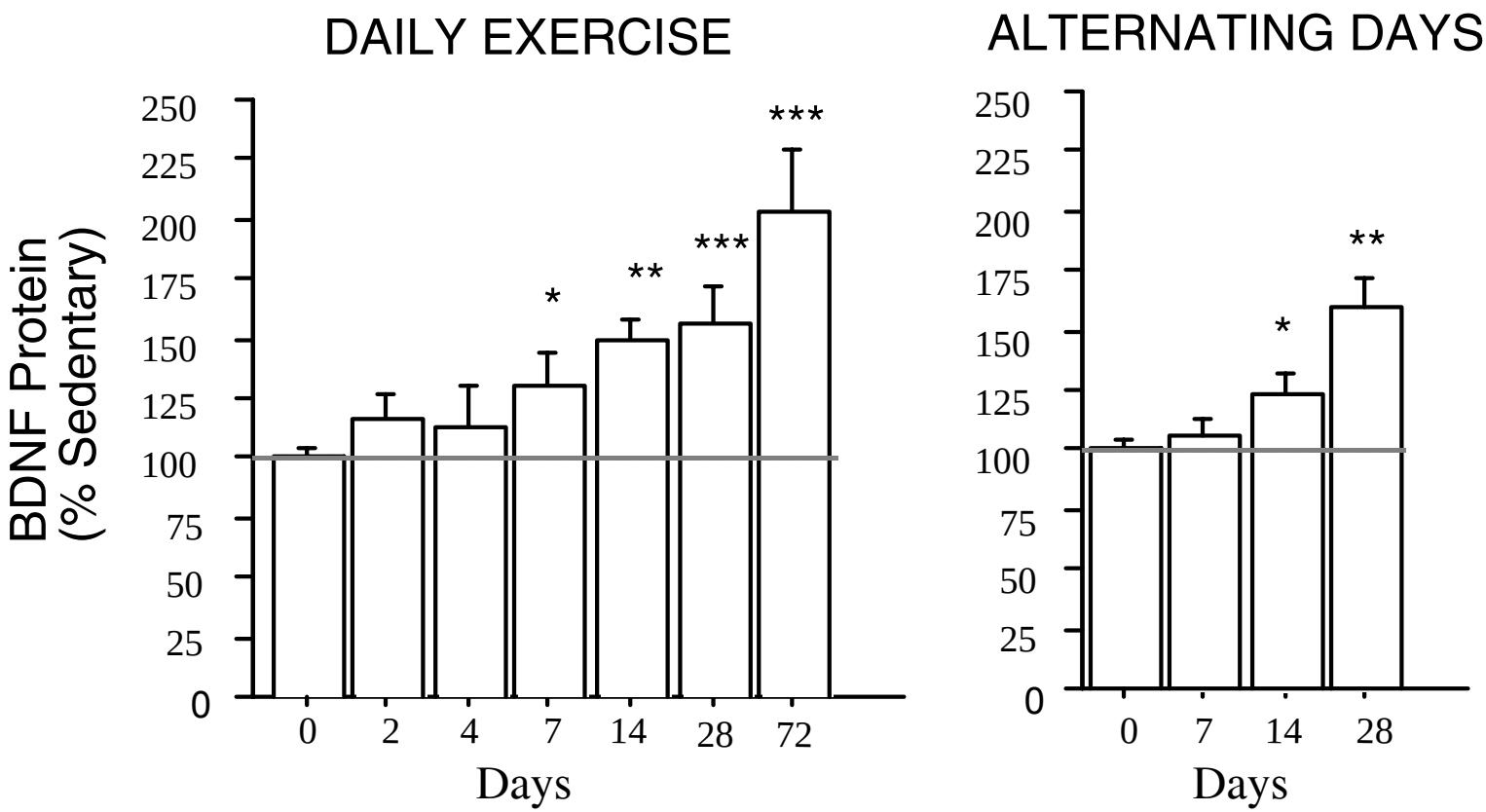




Rats: 1 week exercise (male sprague-dawley, 3 months)

Berchtold et al., 2002

Time course of BDNF Protein Induction

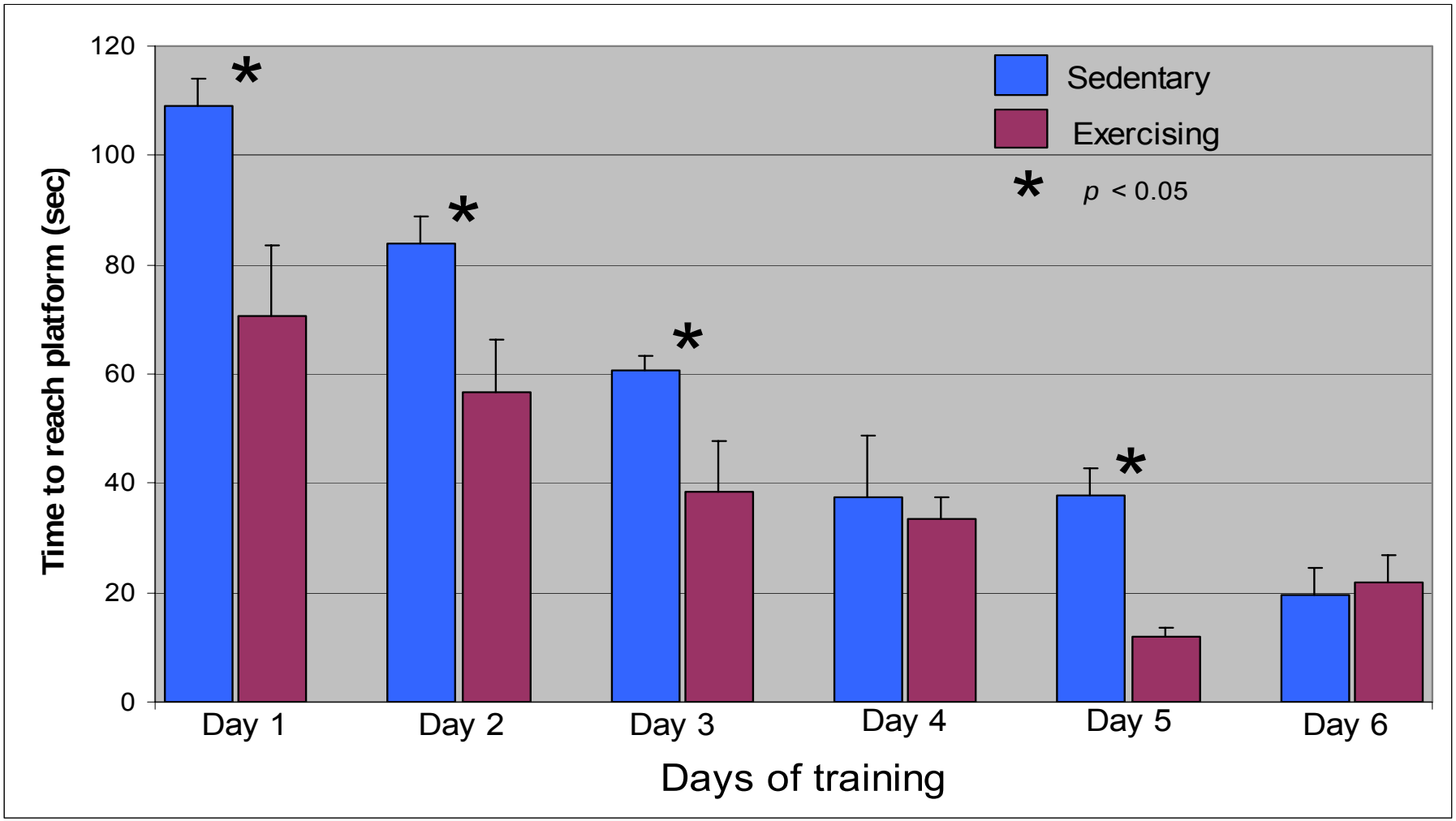


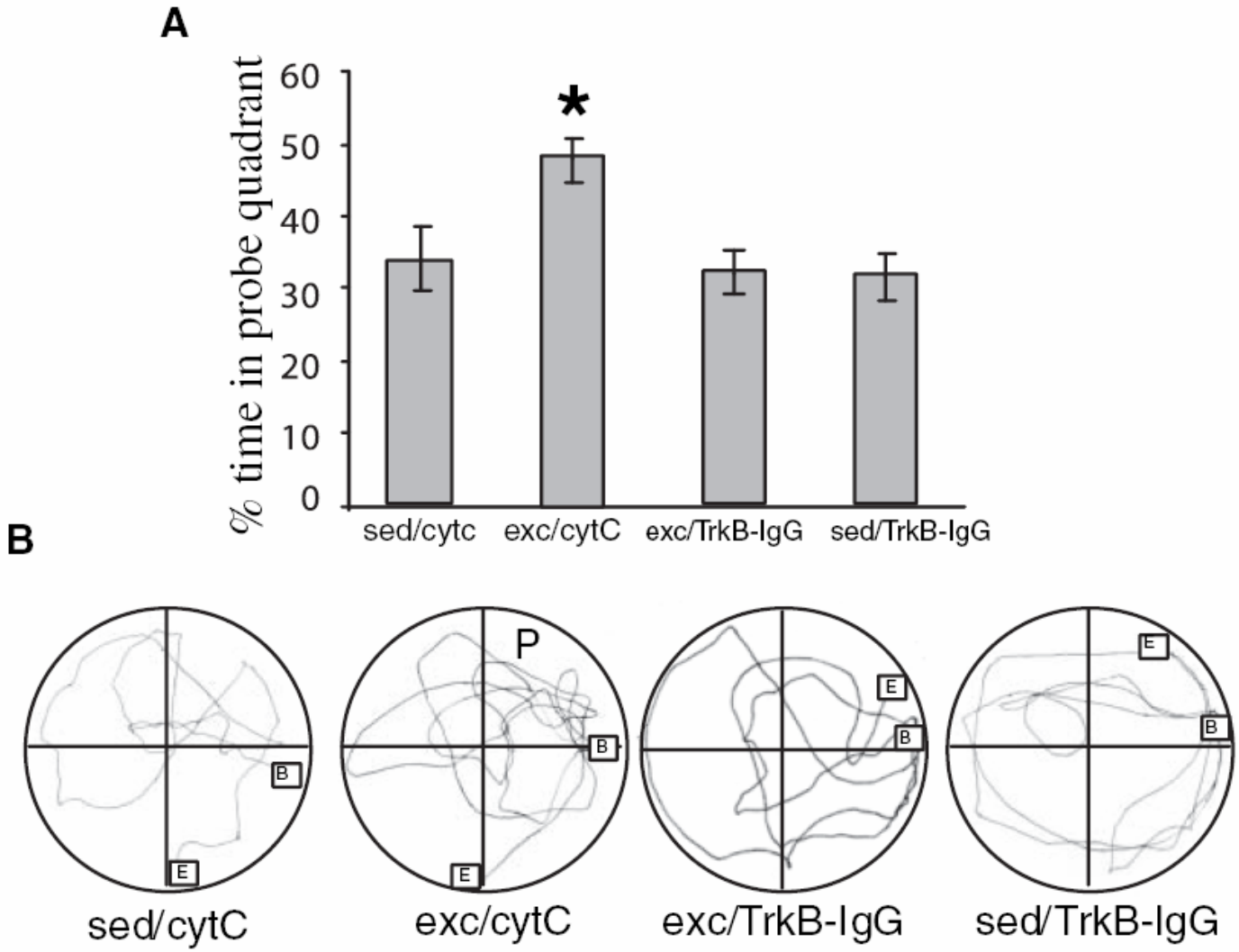
Berchtold, et al., submitted

So..what is the functional significance?

- Learning?
- Stress Relief?

Exercise Enhances Learning in the Morris Water Maze





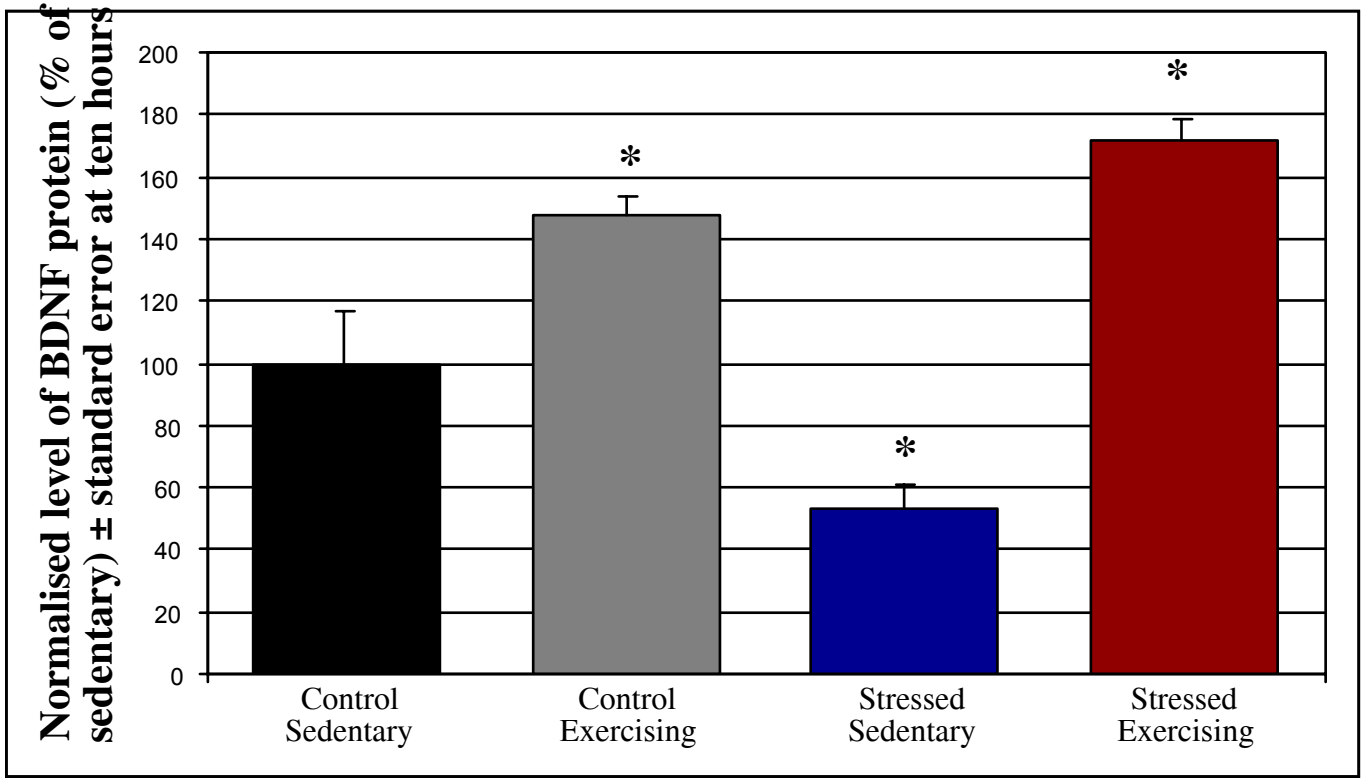
Blocking BDNF action (anti-TrkB) during the exercise period on memory retention using the probe trial on the Morris Water Maze task (Vaynman, et al., 2004)

Can exercise prevent the stress induced reduction in BDNF?

- Animals given 3 wks. of voluntary running
- Subjected to acute immobilization stress
- Circulating corticosterone and brain BDNF measured

Hypothesis: Exercise will offset the effect of acute stress, possibly via a reduction in levels of circulating corticosterone.

At 10 hours post-stress, BDNF is decreased in stressed animals, but remains elevated in animals that had prior exercise



* Significantly different ($p<0.05$) from control sedentary

Many plasticity genes are regulated by BDNF,e.g.,

- Synapsin: Regulates presynaptic vesicle availability
  Modulates neurotransmitter release into synapse
  - » Block TrkB in vivo suppresses exercise-induction of synapsin mRNA (Gomez-Pinilla, 2003)
- CREB: Transcription factor, drives downstream gene expression
  Important in LTP, learning and memory
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- NR2b: subunit of glutamate receptor (NMDA)
  Overexpression enhances LTP and improves learning
  - » Slice culture: BDNF increases NR2b protein
- NARP: Trafficking/insertion of glutamate receptors in PSD, critical to LTP and learning
  - » Slice culture: BDNF increases NARP protein
- COX-2: traditionally known for immune function
  Role in plasticity: localized to dendrites
  - » Slice culture: BDNF increases COX-2 protein

Practical Questions

- How long lasting is the increase after stopping exercise?
- How frequent is necessary
- Can the increase be recovered rapidly if exercise is stopped for a peroid?

Is there a molecular memory for exercise?

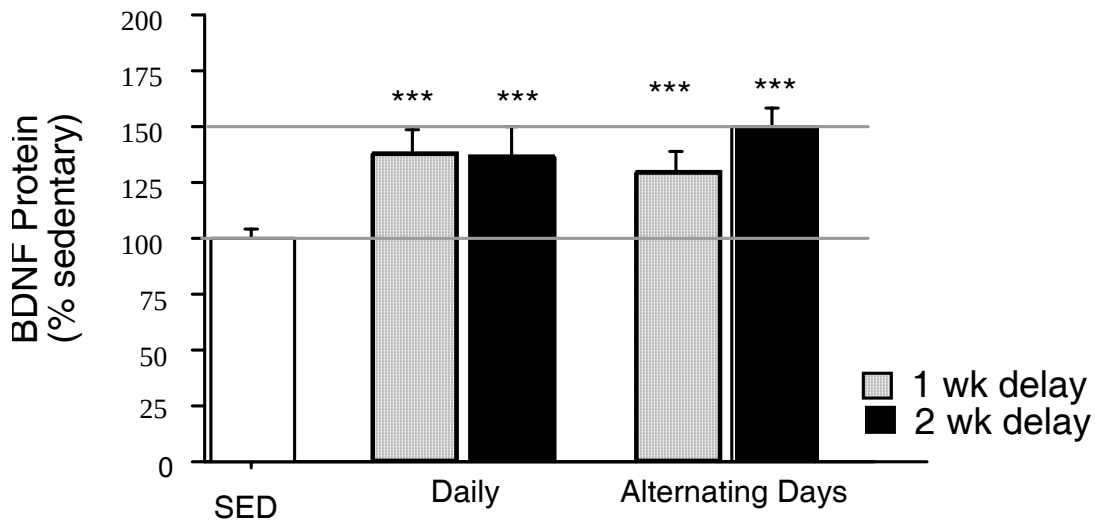
- Many of the gene changes including CREB are linked to learning and memory
- Is the experience of exercise encoded so to allow the brain to learn to respond?

Thus, if so exercise may prime the brain to respond to experiences, and induce a “state of readiness”.

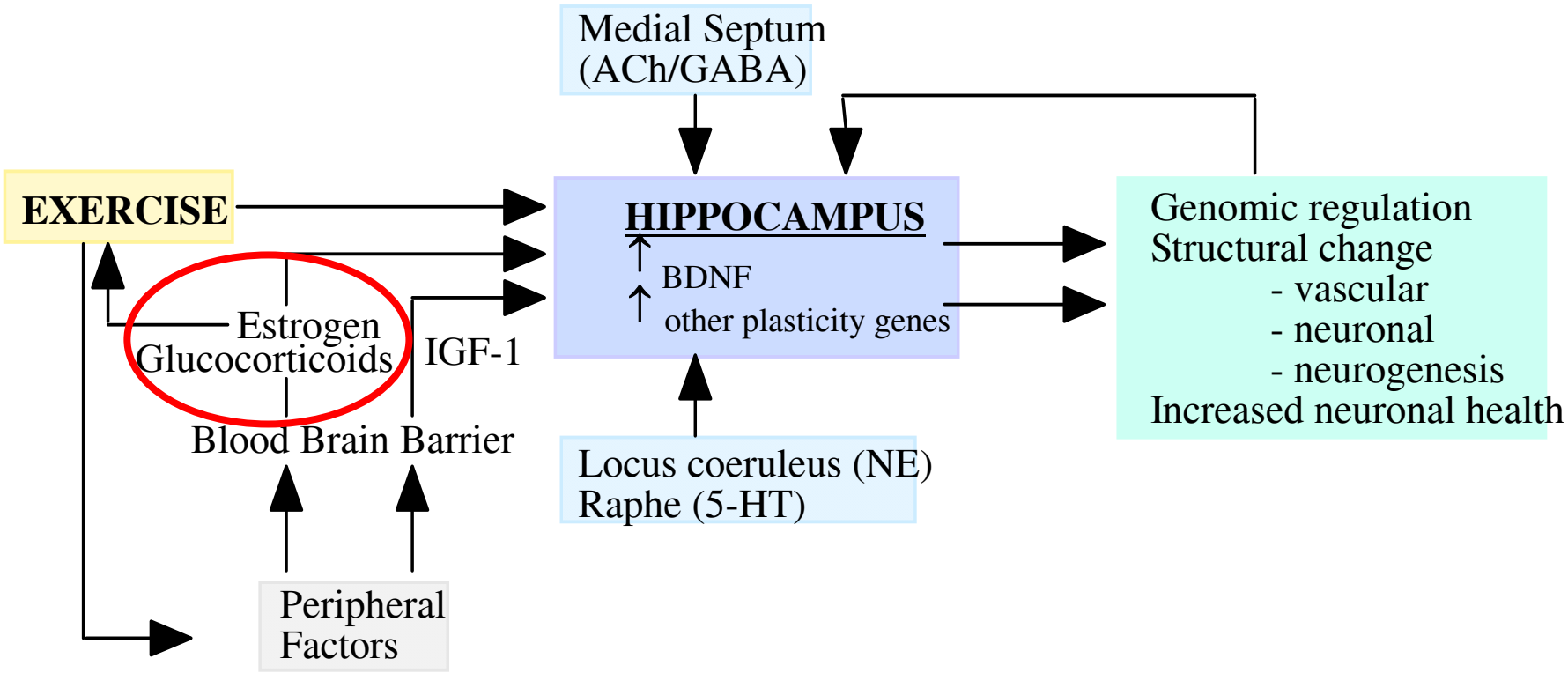
How Often to Exercise?: Is there a Molecular Memory Exercise

Paradigm:

- 14 days of exercise:
  - Daily (during 2 weeks)
  - Alternating (during 4 weeks)
- Wheels locked:
  - 1 week, 2 weeks
- Second short run period (2 days)
- **Note: 2 days exercise alone is not sufficient to increase BDNF**

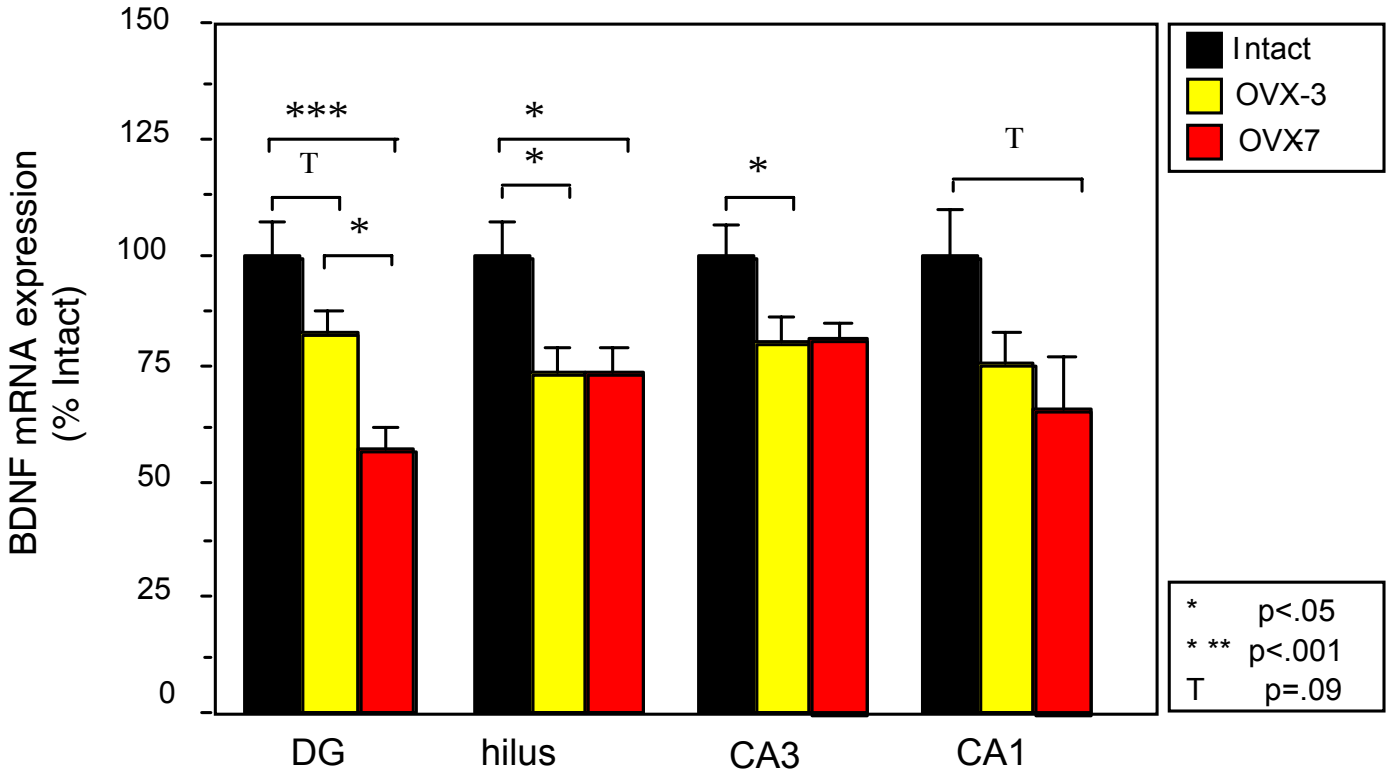


- Prior Exercise Primes subsequent BDNF Responsiveness
- Priming effect endures at least 2 weeks
- Equivalent Secondary Responsiveness if prior exercise is Daily Regime or Alternating Days of Exercise

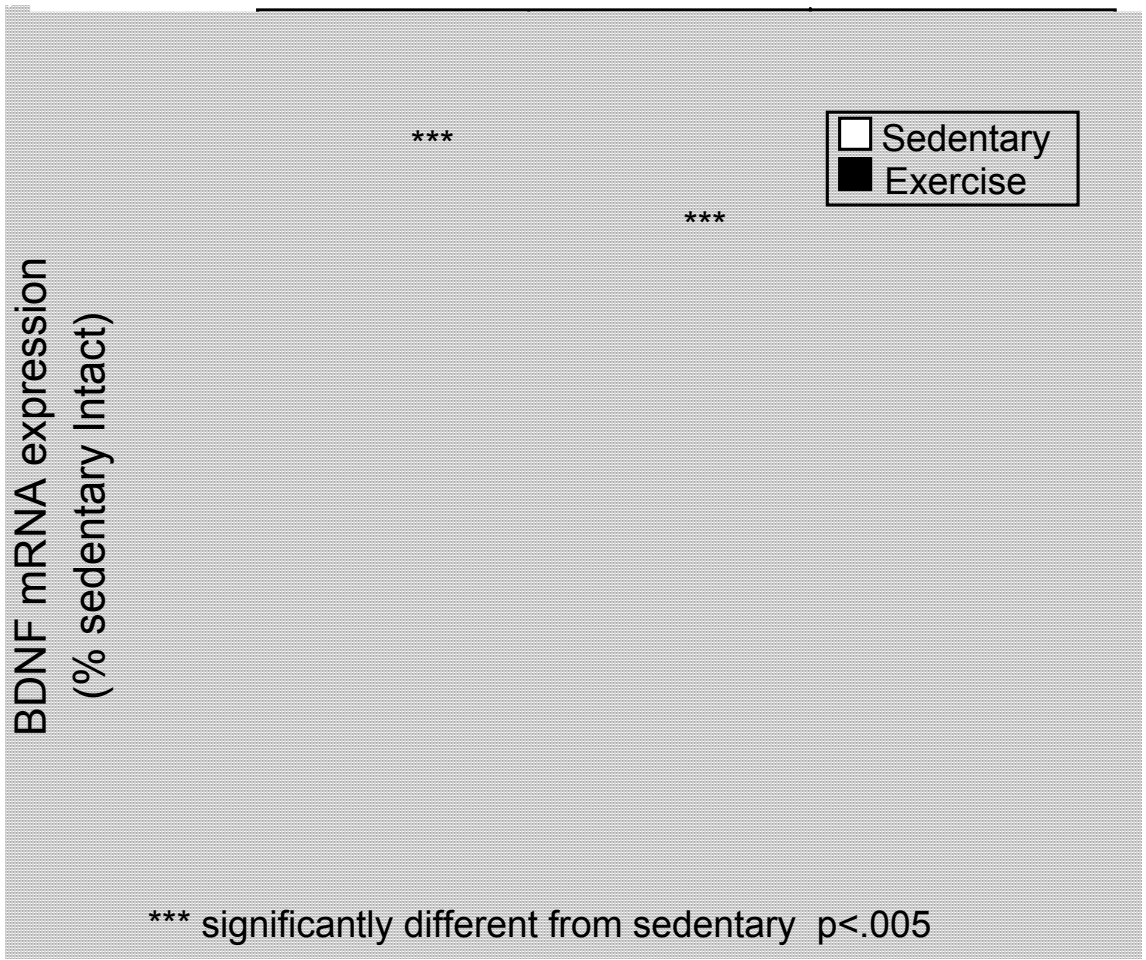


Cotman & Berchtold (2002)

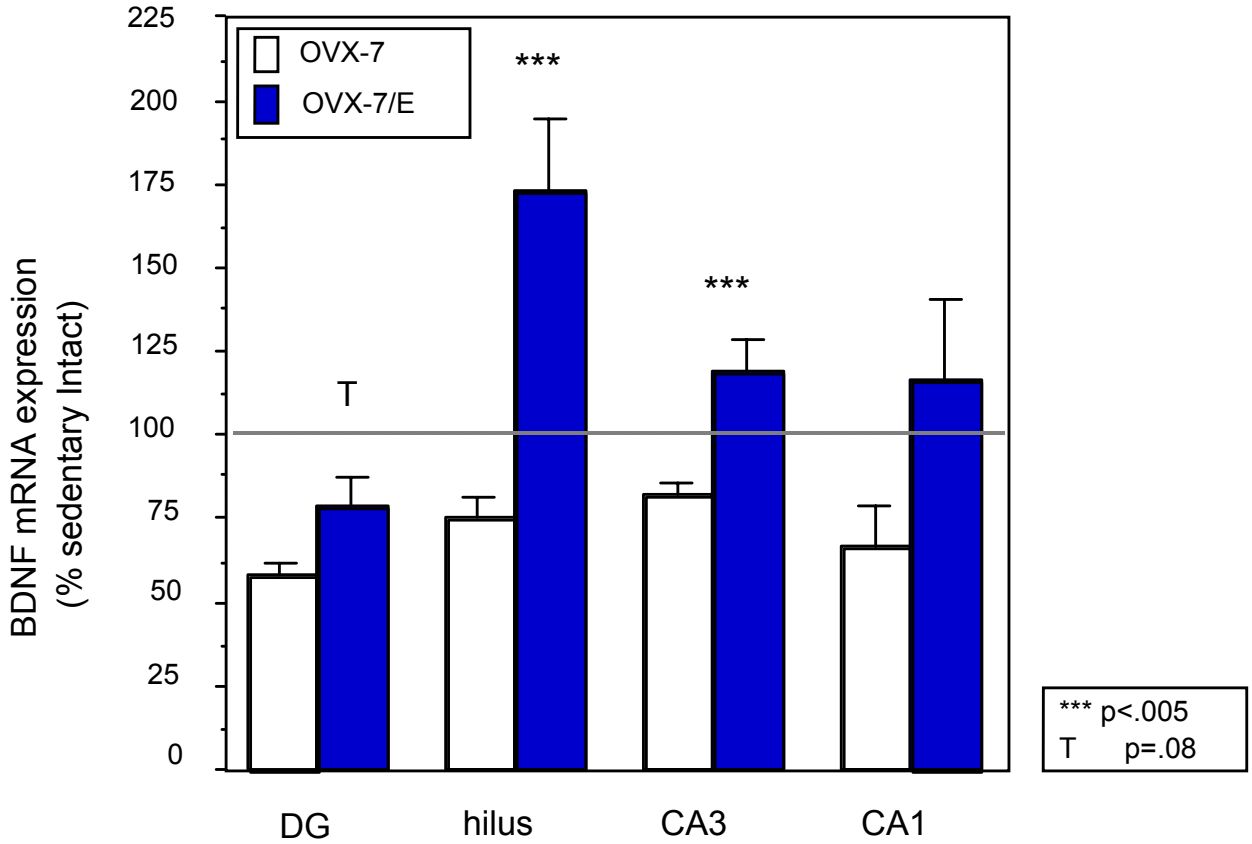
Estrogen-deprivation reduces baseline BDNF gene expression (Berchtold, etal., E.J. of Neurosc., 2001)



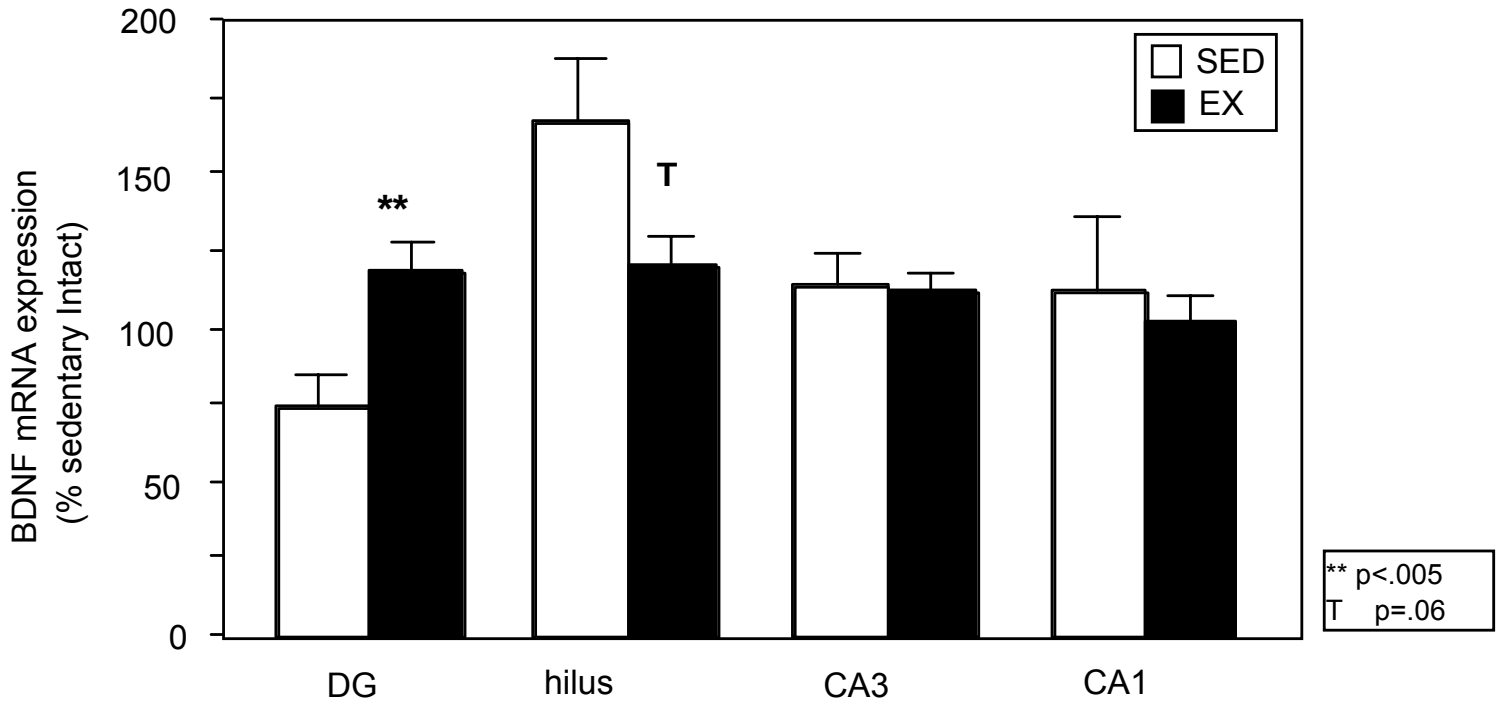
Exercise-induced BDNF increase is lost after 7 weeks of estrogen deprivation



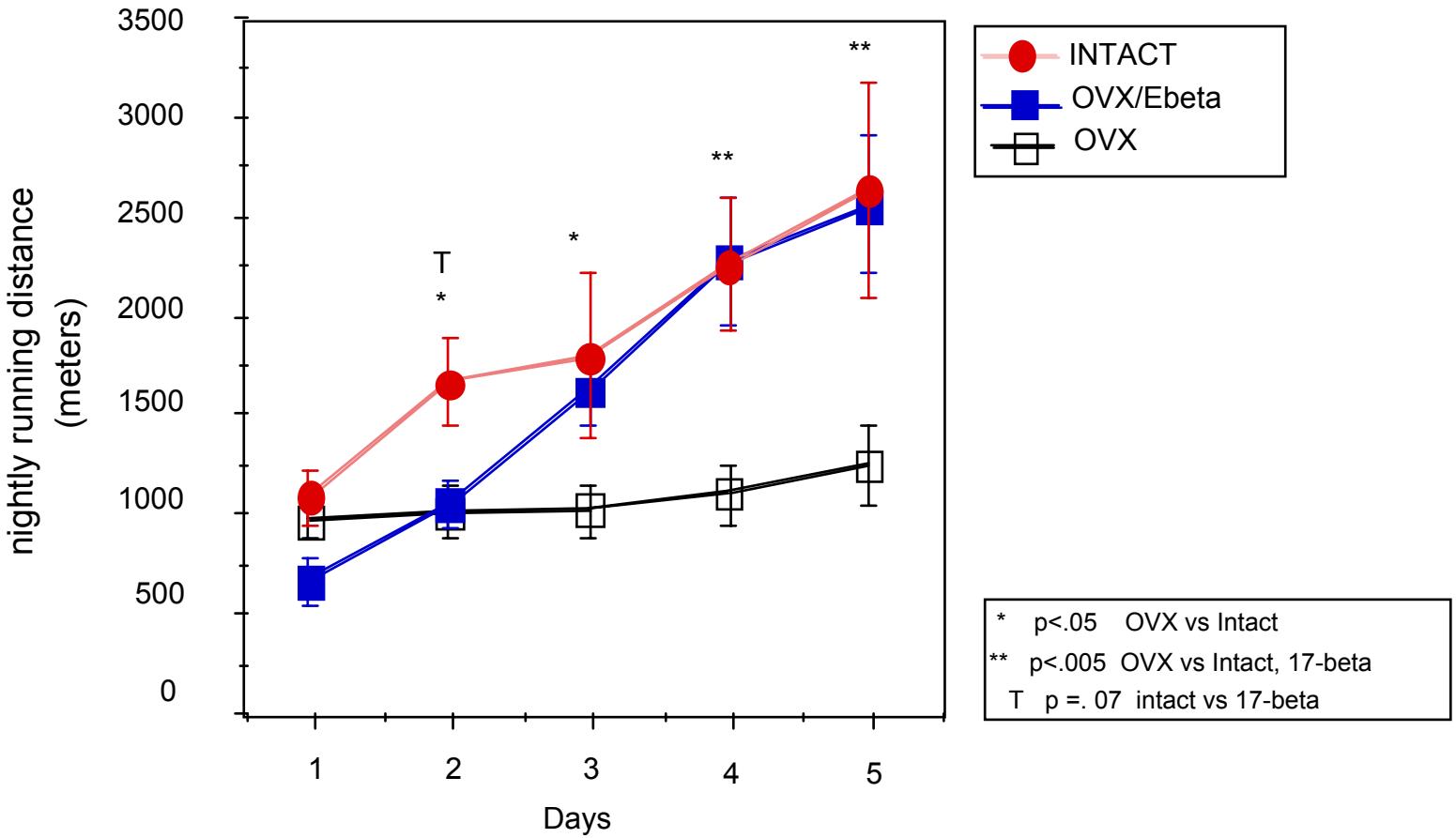
Estrogen-replacement increases BDNF mRNA level

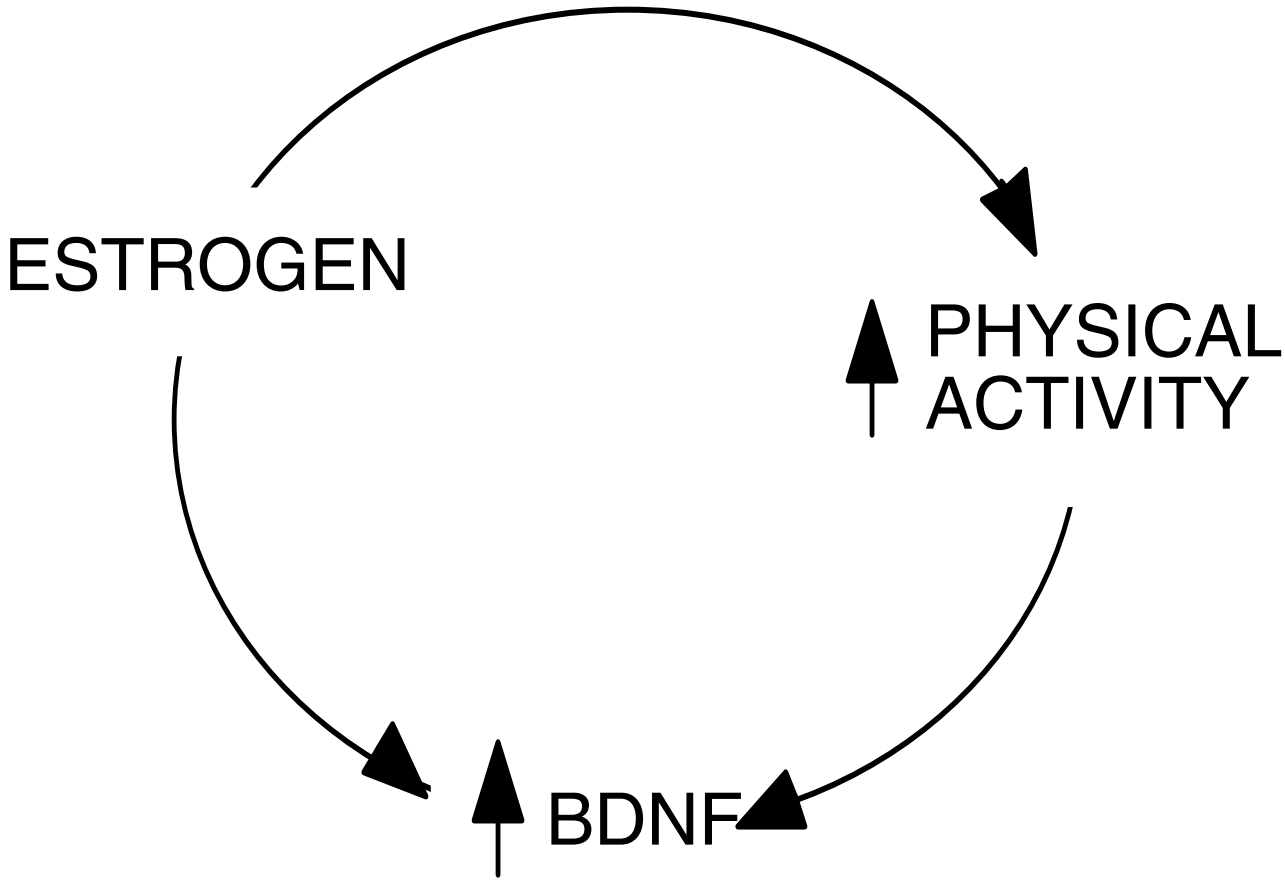


Exercise Further Increases BDNF, Specifically in the DG



Hormone replacement (17-beta Estradiol) Restores Running Behavior



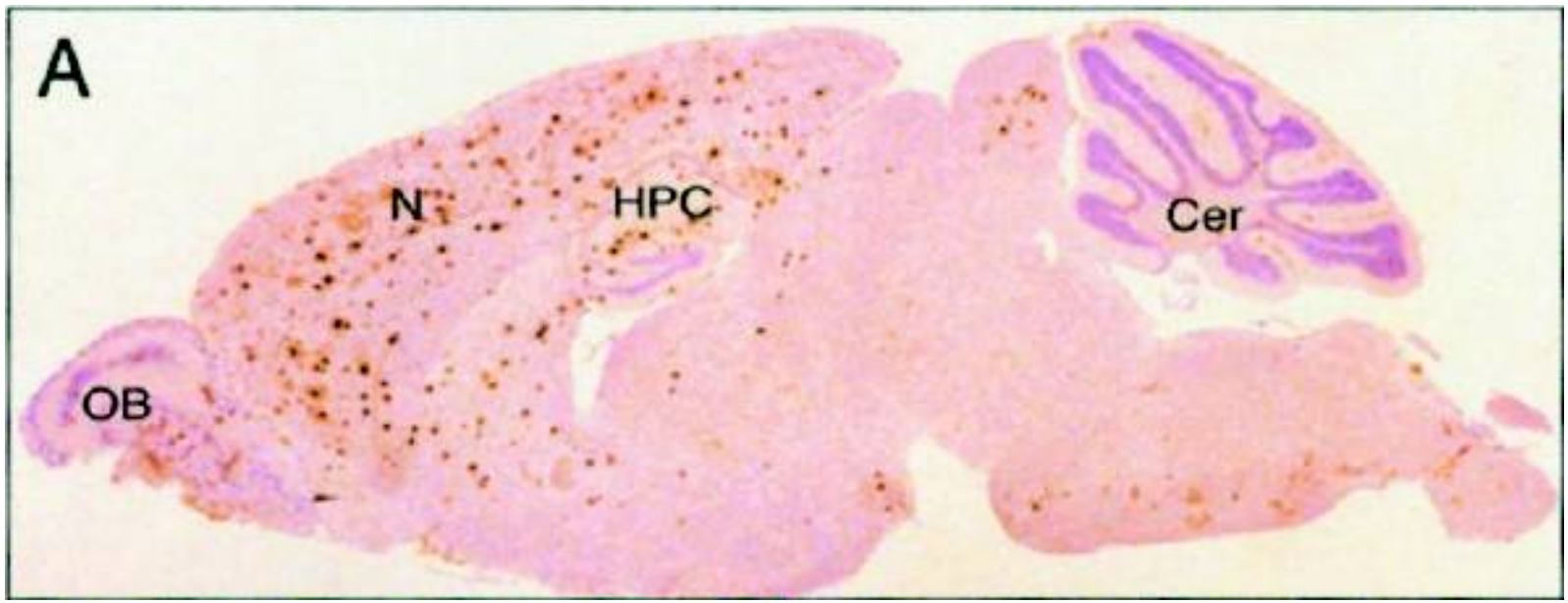

ESTROGEN
PHYSICAL ACTIVITY
BDNF

Is exercise effective in AD transgenic models ?

- Will voluntary running improve learning and memory?
- Stimulate neurogenesis?
- Reduce β-amyloid in the brain?

Animal model

Widespread plaque deposition, including the hippocampus and cortex



Chishti et al., JBC 276: 21562-21570, 2001.

Voluntary Exercise Paradigm
(Adlard, etal., 2005)

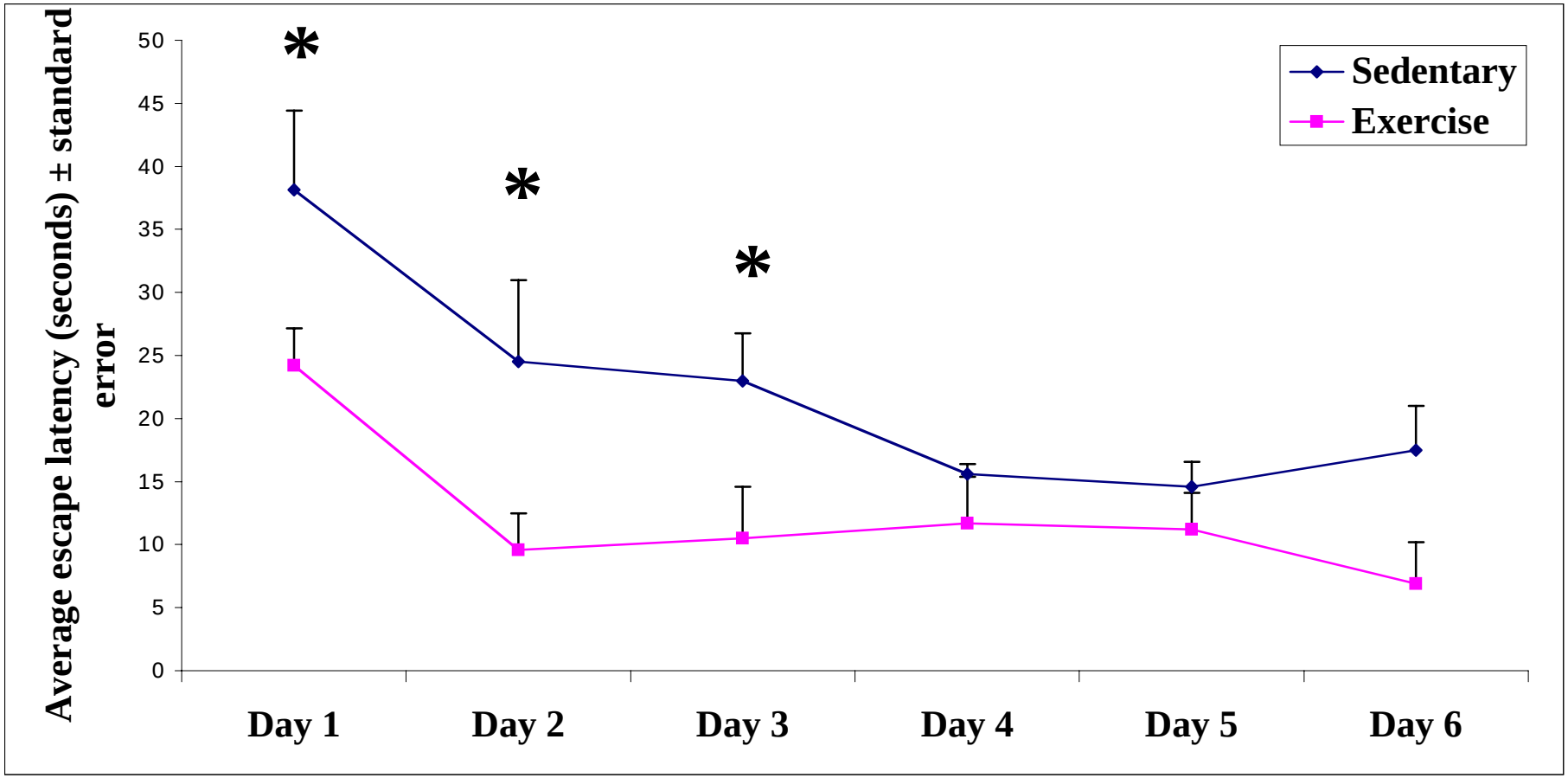
- Utilized TgCRND8 mouse model

- Voluntary access to running wheels (animals run ~3 miles/day)

- Short-term running
  - start at 6 weeks of age
  - sacrifice four weeks later

- Long-term running
  - start at 6 weeks of age
  - sacrifice 5 months later

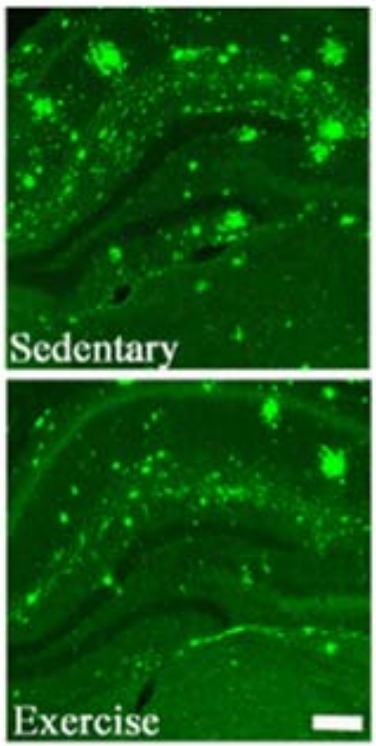
Exercise improves the performance of TgCRND8 animals in the Morris water maze

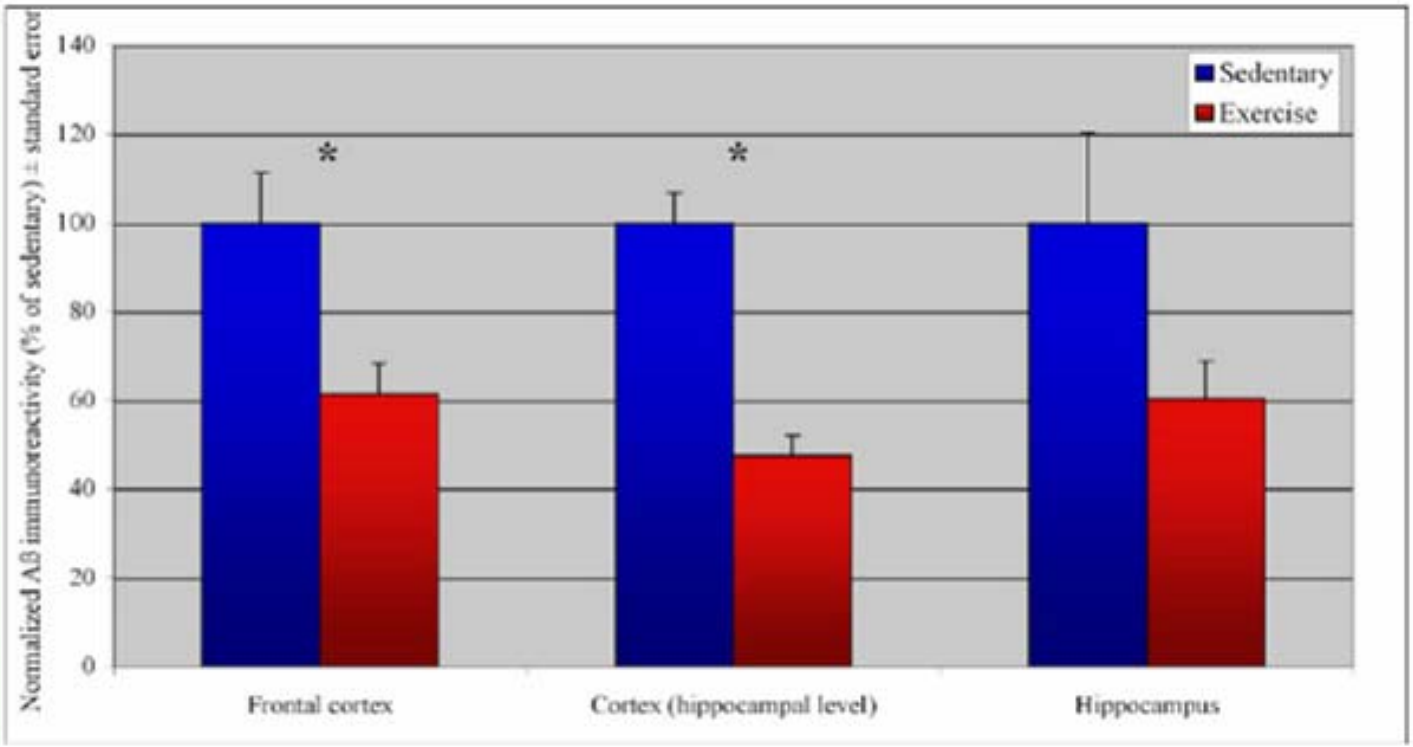


* p<0.02

Long-term running reduces ß-amyloid load in TgCRND8 animals

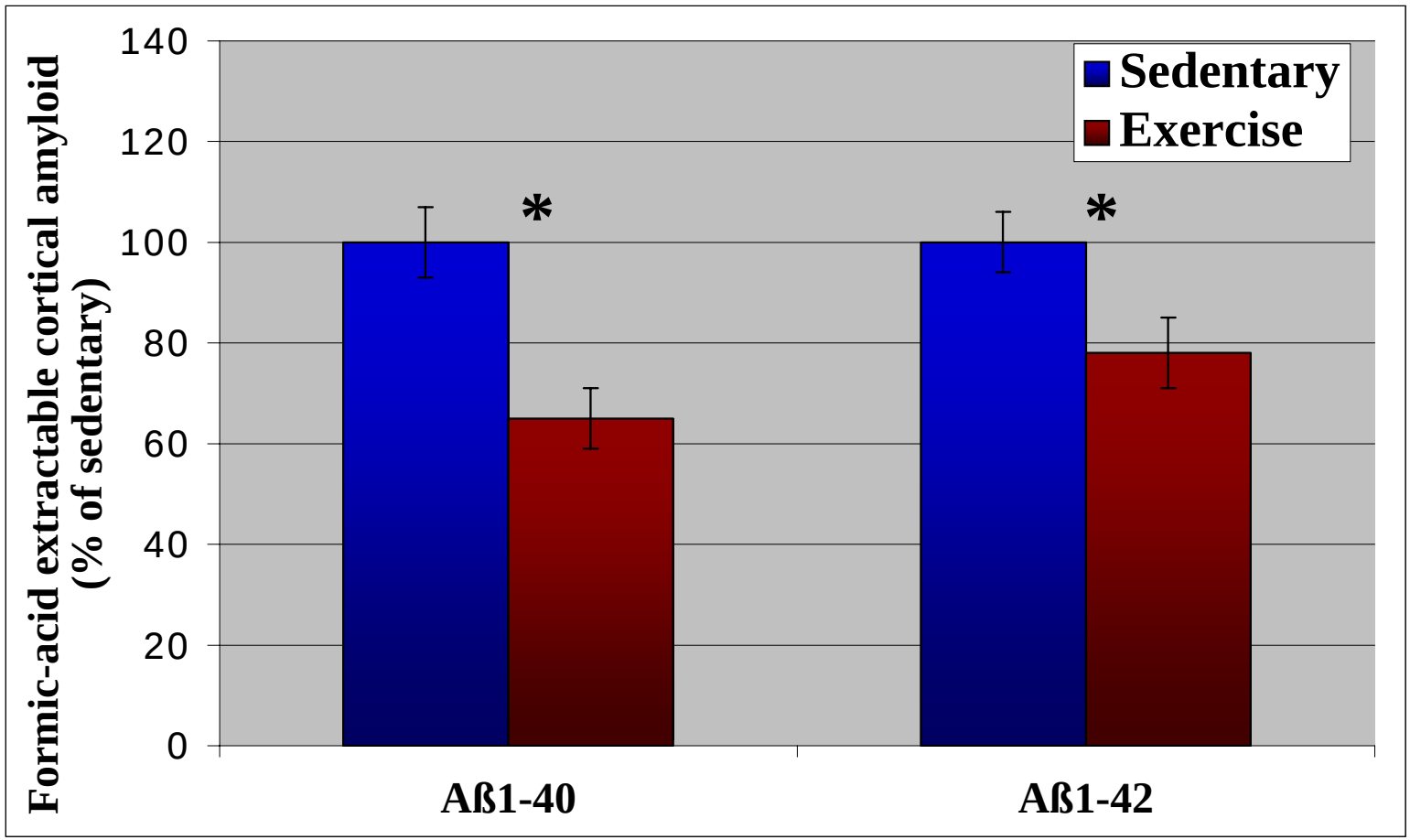
(by immunohistochemistry)



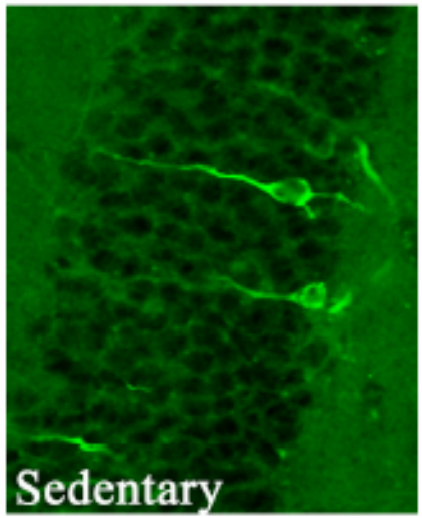


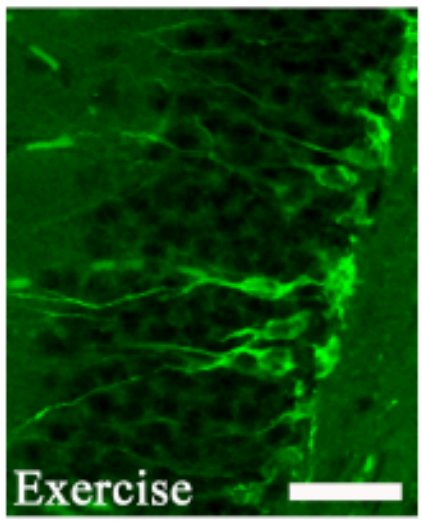
Long-term running reduces ß-amyloid load in TgCRND8 animals

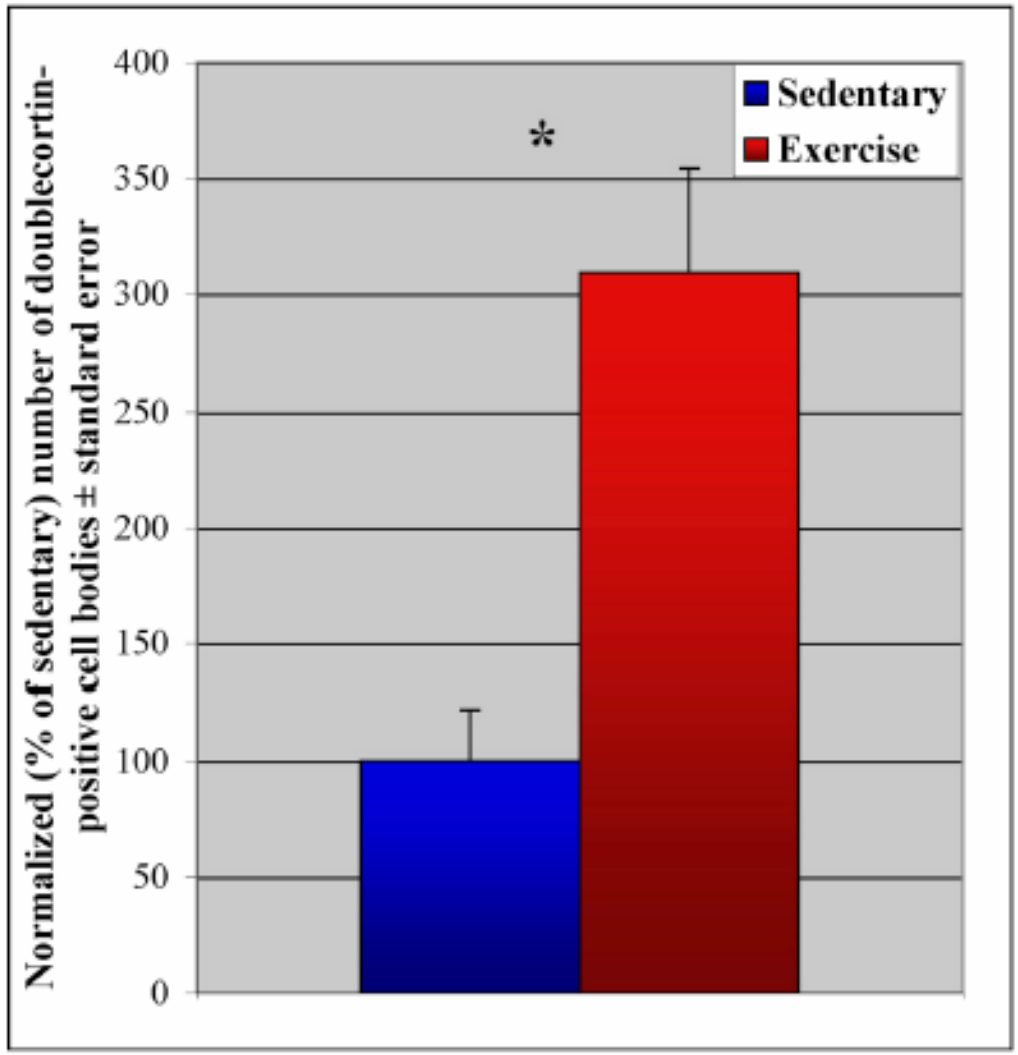
(by ELISA)



Long-term running enhances neurogenesis in TgCRND8 animals







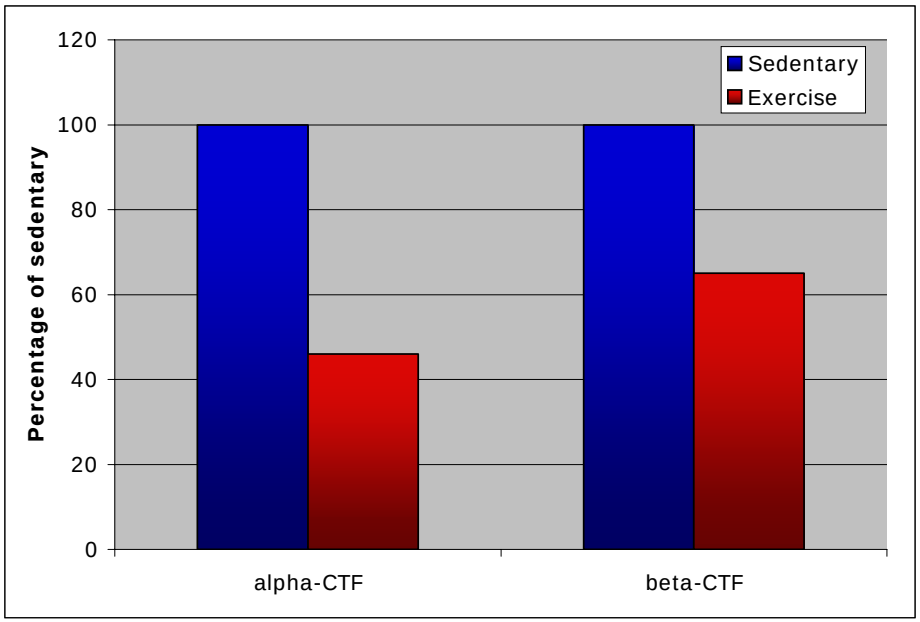
Mechanism: Long-term running had -

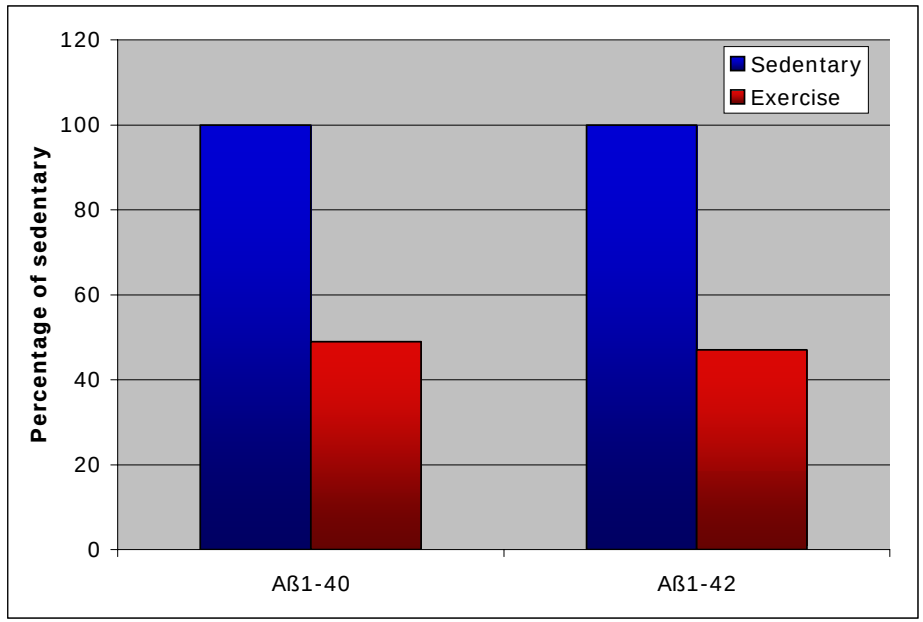
- no effect on steady-state levels of the amyloid precursor protein, APP

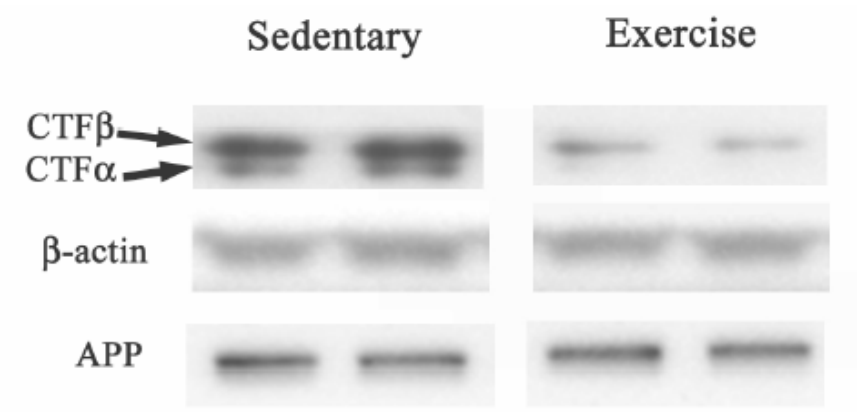
- no effect on secretase activity levels (α, β, γ)

Does short term running affect APP processing?

Short-term running mediates APP processing







- no effect on total APP
- no effect on secretase activity (α, β, γ)
- no effect on neprilysin or IDE

Summary

- BDNF increases with exercise in the hippocampus within a few days and lasts
- BDNF induction can be rapidly restored by a brief period of exercise even after exercise is stopped for weeks
- Exercise improves the rate of learning
- Exercise reduces β-amyloid in the hippocampus and cortex
- Exercise alters APP processing

Summary Part 2

- Exercise in a transgenic AD mouse improves learning
- Exercise reduces β-amyloid in the hippocampus and cortex
- Exercise alters APP processing

Diet? What effect does an antioxidant diet have on cognition?

Can antioxidants and/or Exercise/Environmental Enrichment Delay the Development of Age Dependent Cognitive Dysfunction and Neuropathology in Canines?

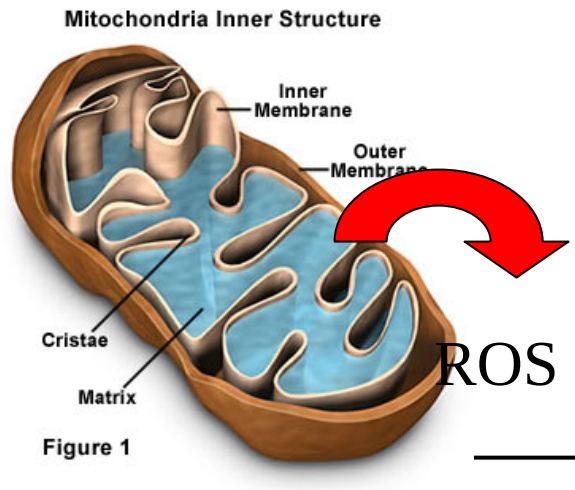
Canine Antioxidant Diet

- Antioxidants

- dl-alpha tocopherol acetate-1050 ppm (20 mg/kg - 800 IU
- Stay-C (ascorbyl monophosphate)-100 ppm
- Spinach, carrot granules, tomato pomace, citrus pulp, grape pomace - 1% each in exchange for corn (Increased ORAC by 50%)

Mitochondrial cofactors

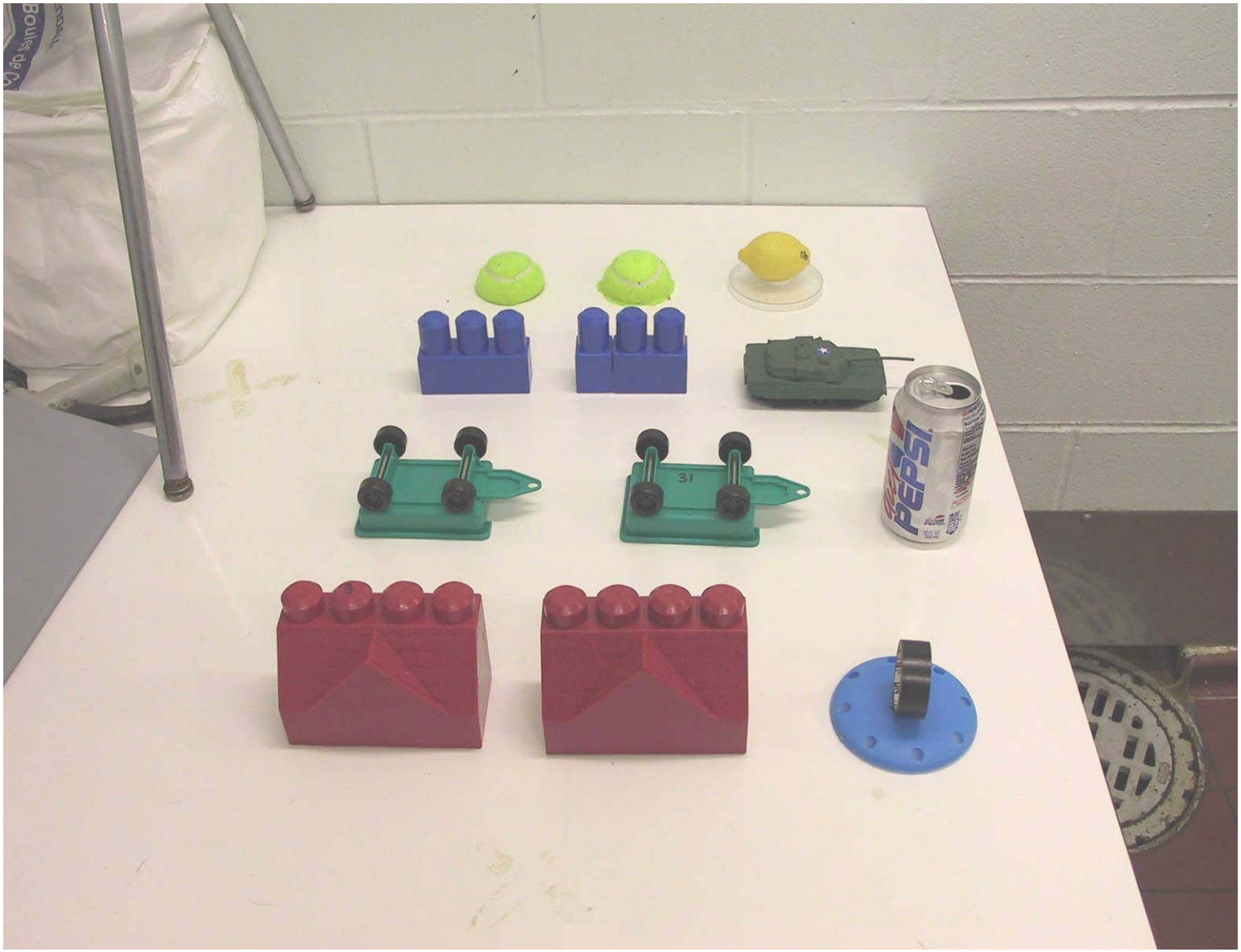
- dl-Lipoic acid - 135 ppm (2.7 mg/kg)
- l-carnitine,Acetyl-car-300 ppm (6 mg/kg)



Enrichment Protocol

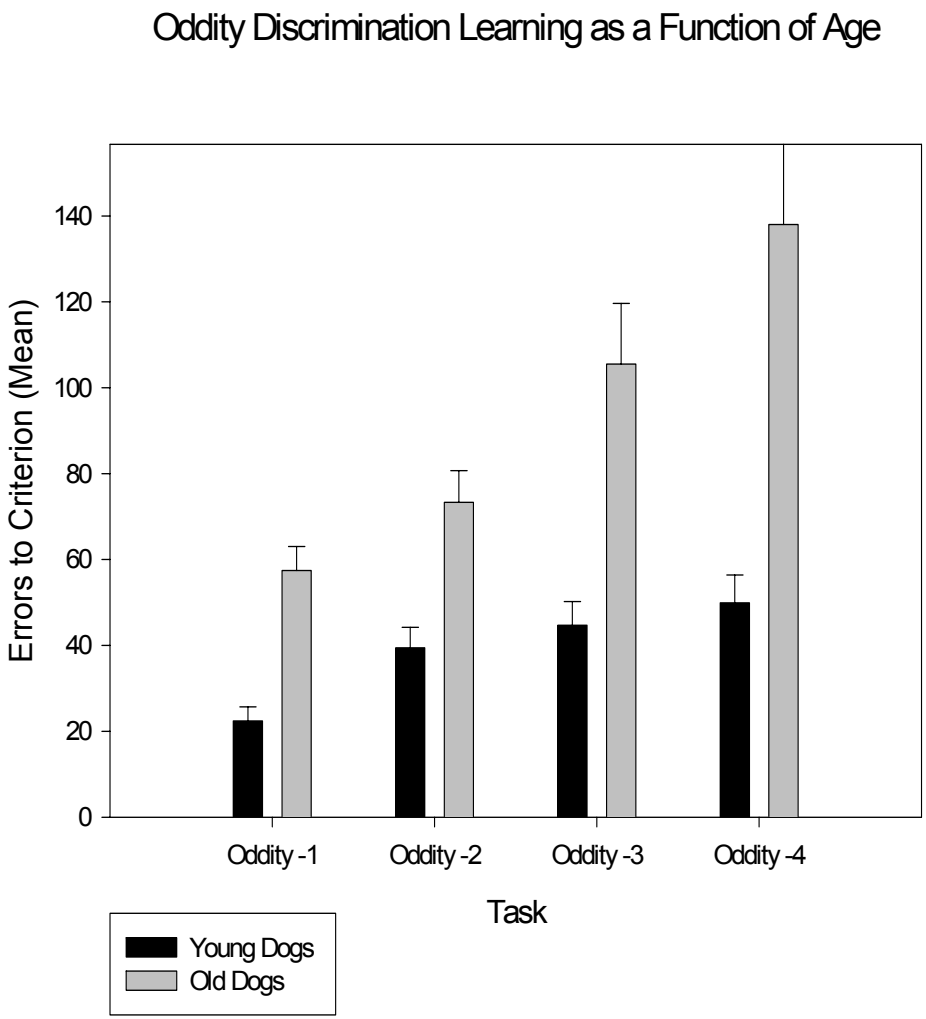
- Play toys
- kennelmate
- 3x20 min walks
- additional cognitive experience

Controls

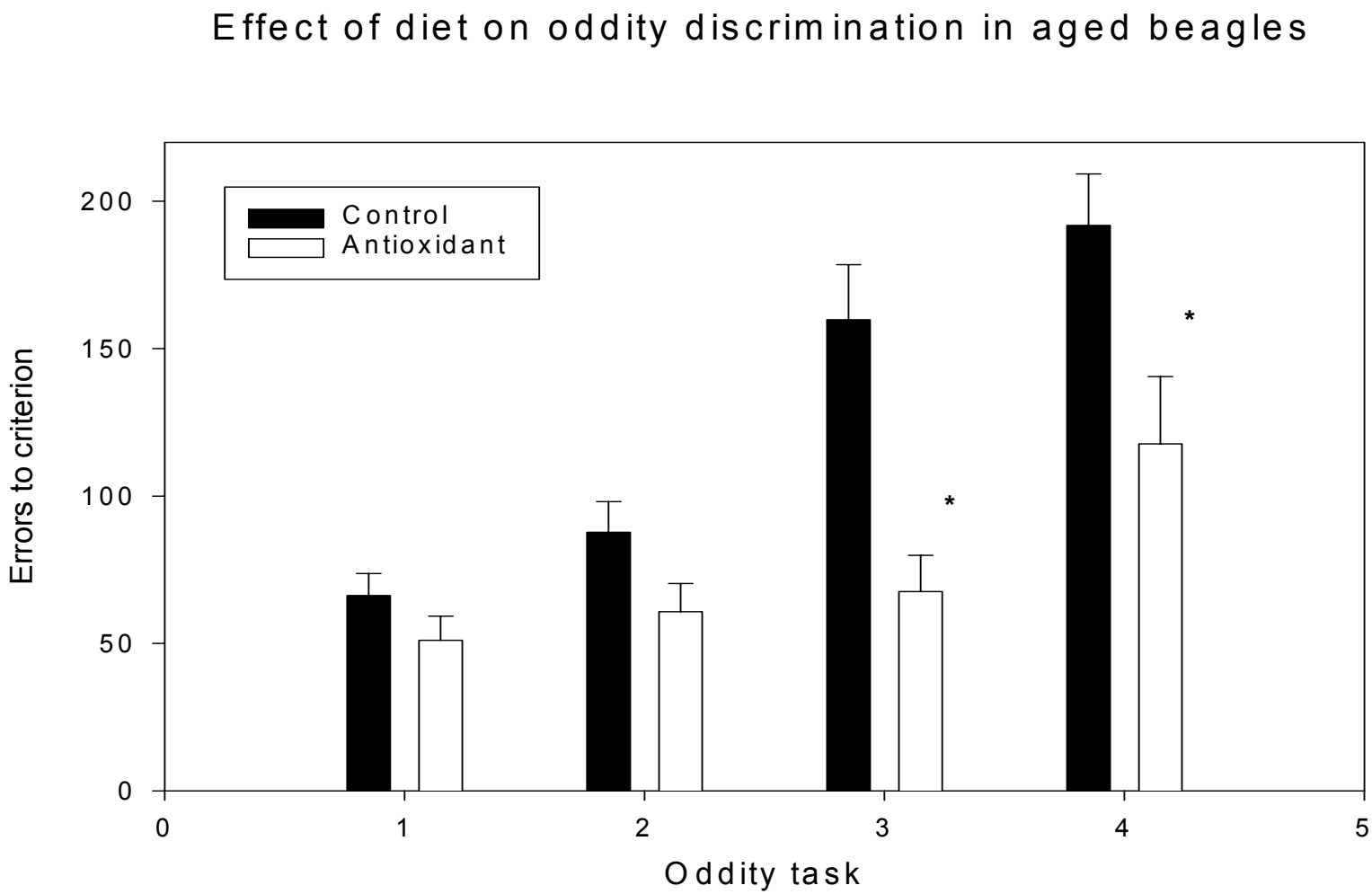


6 months

Learning Is Impaired in Old Canines



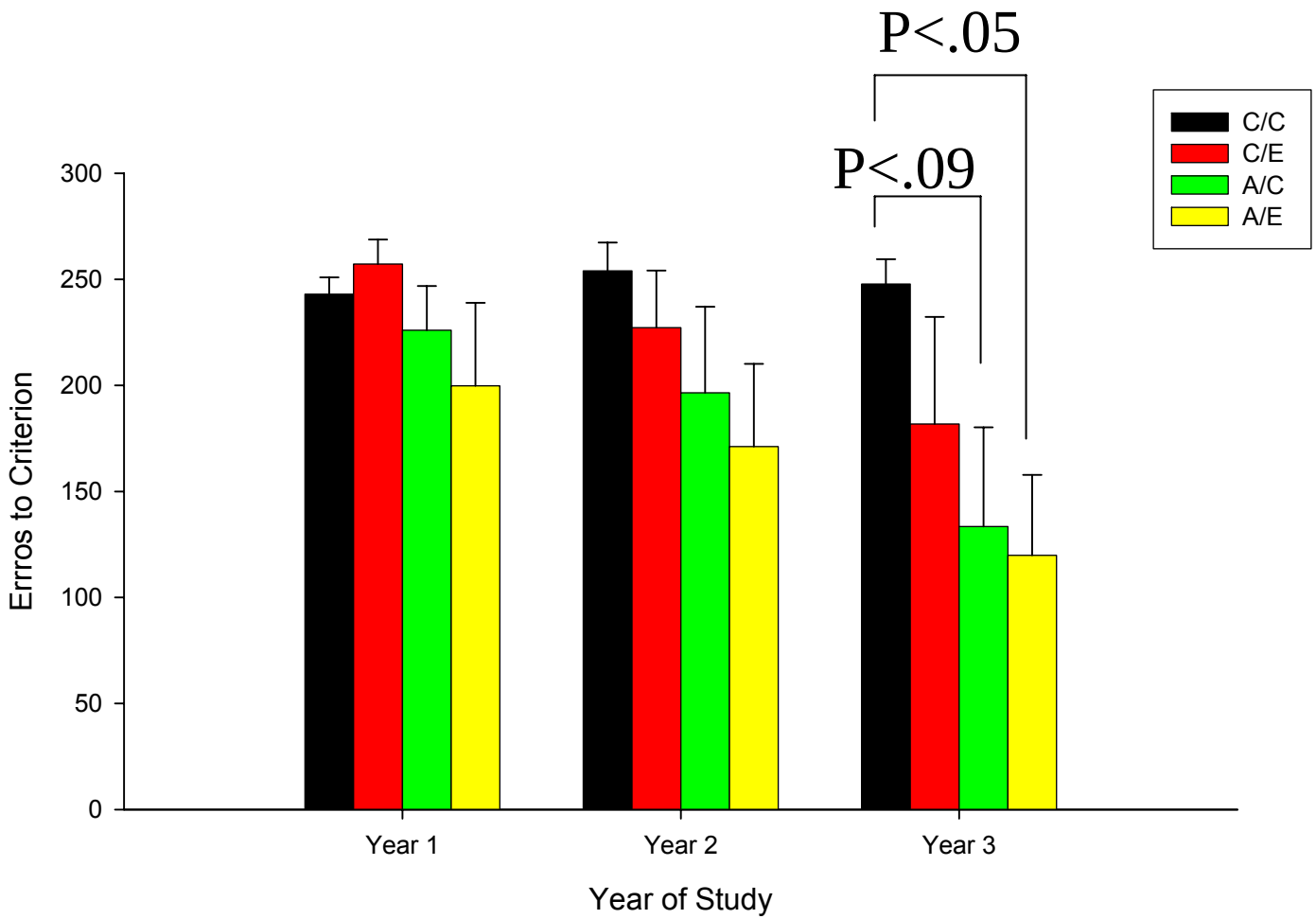
Aged dogs make more mistakes as task complexity increases .



Diet fortified animals make few mistakes as task difficulty increases

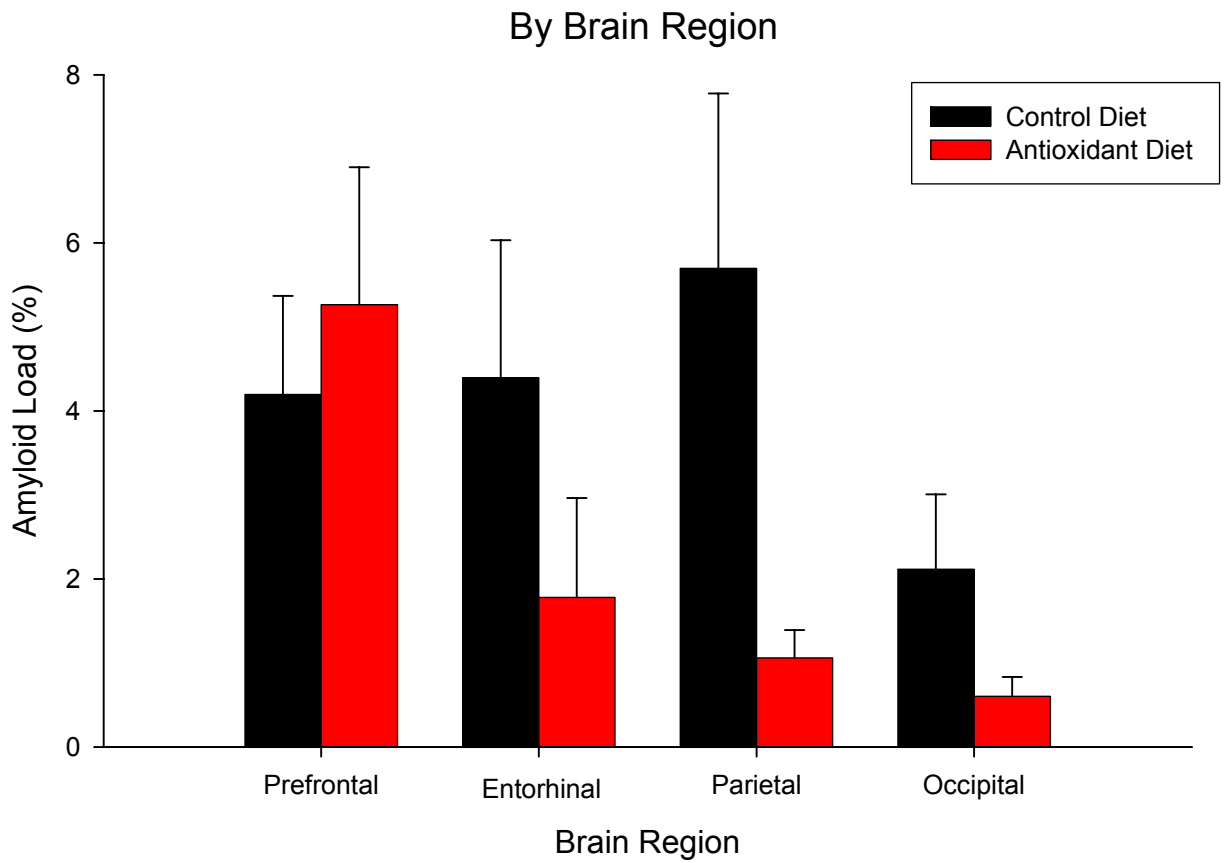
Is the intervention able to “reverse” age related cognitive dysfunction?

Spatial Memory and Treatment



What effect, if any, do the treatments have on brain pathology?

Effect of Antioxidant Diet on Total Amyloid Load (6E10)



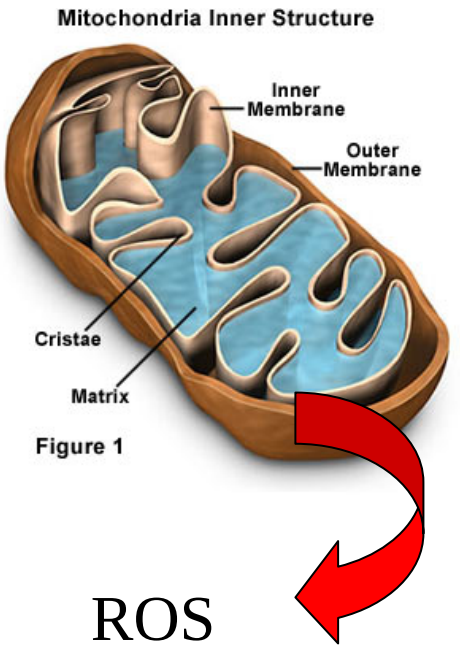
Conclusion

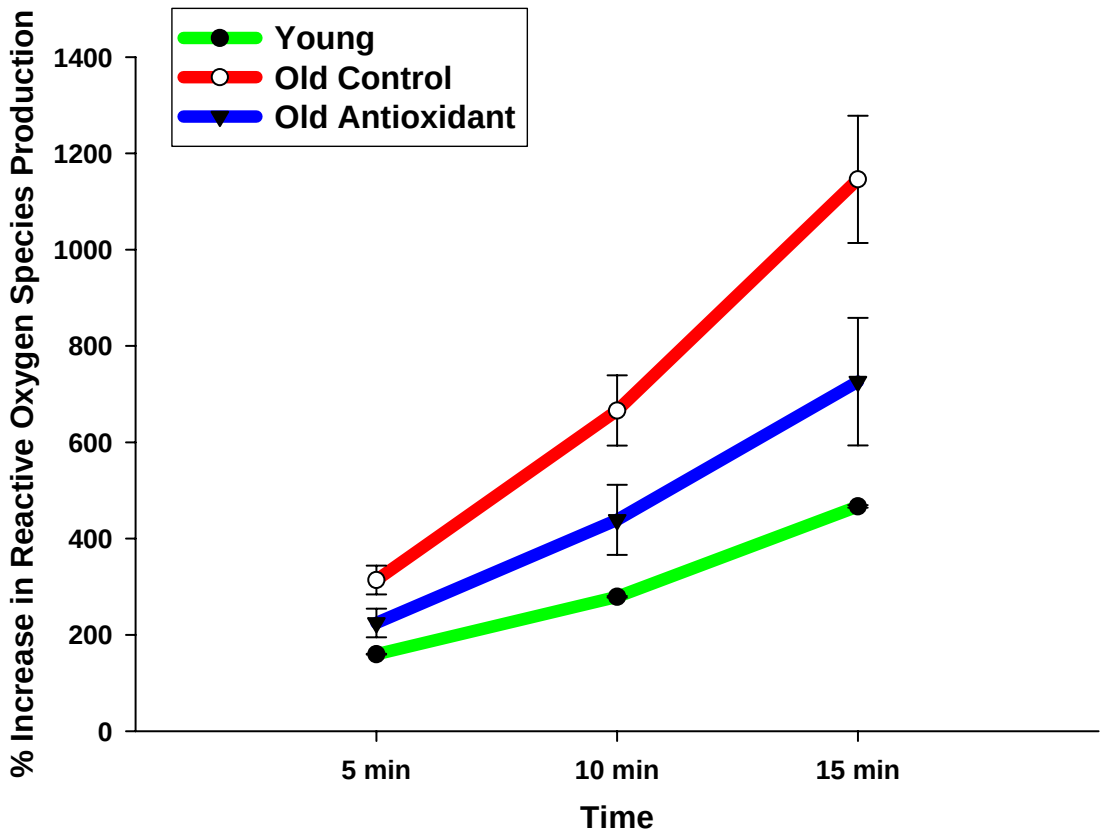
- A growing clinical literature suggests that exercise and diet can delay the onset of cognitive decline and AD
- Animal models show that exercise induces BDNF, a key plasticity and neuroprotecive factor
- Animal models show that exercise and diet can reduce β-amyloid levels

Summary Part 3

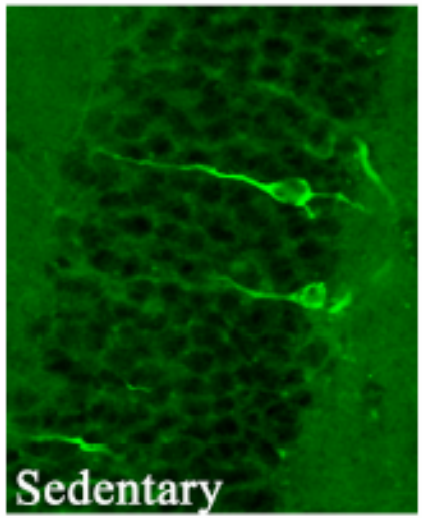
- A diet enriched in mitochondrial antioxidants improves learning in aged dogs
- Reduces β-amyloid accumulation
- Diet plus environmental enrichment is better than either alone

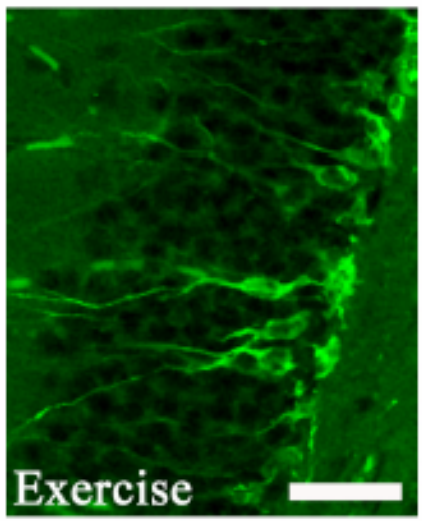
Reduced reactive oxygen species (ROS) production by mitochondria in treated aged dogs

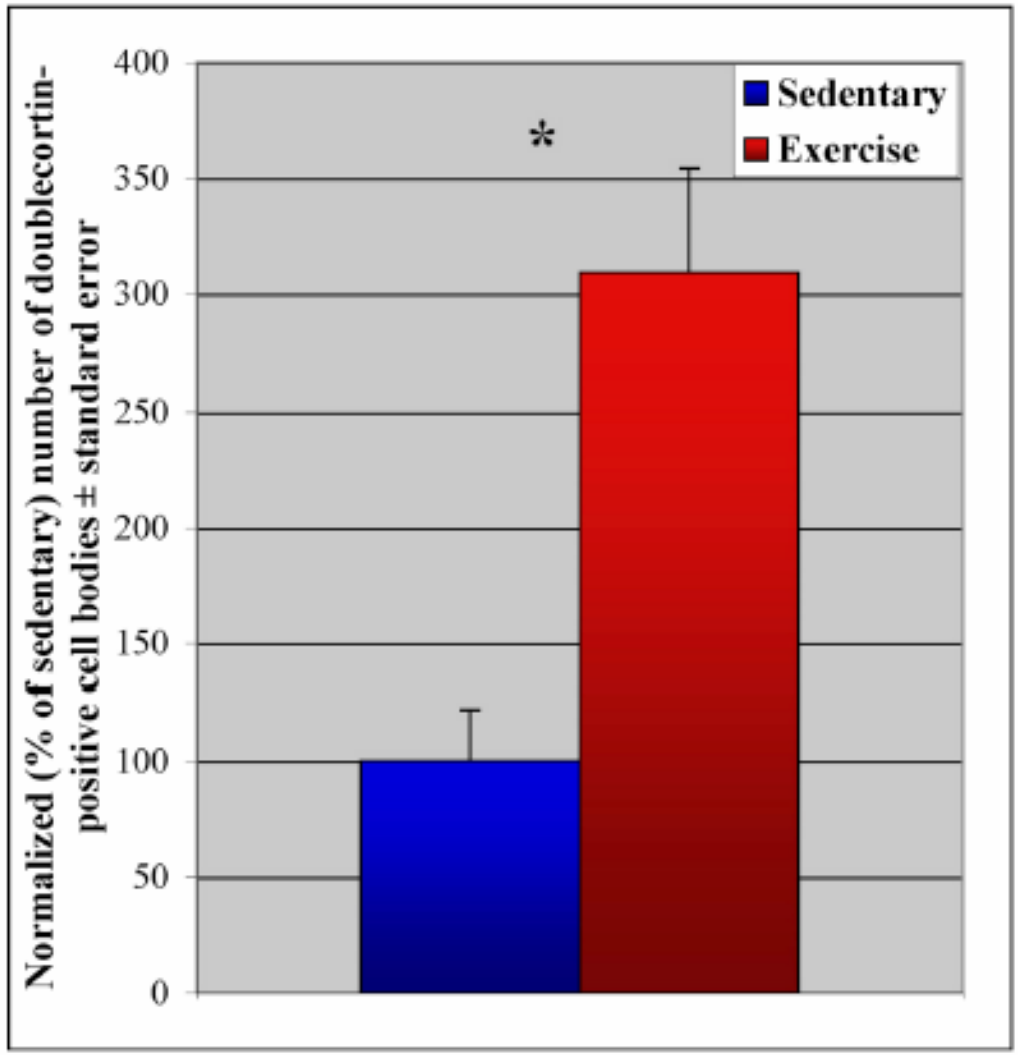




Long-term running enhances neurogenesis in TgCRND8 animals







Is there a molecular memory for exercise?

- Exercise may prime the brain for learning and induces a state of readiness?

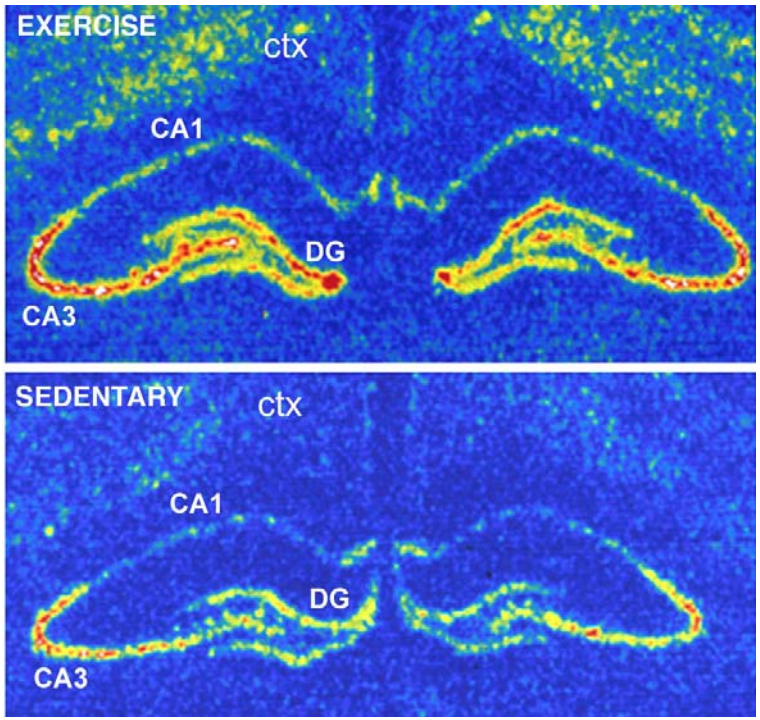
Is there a molecular memory for exercise?

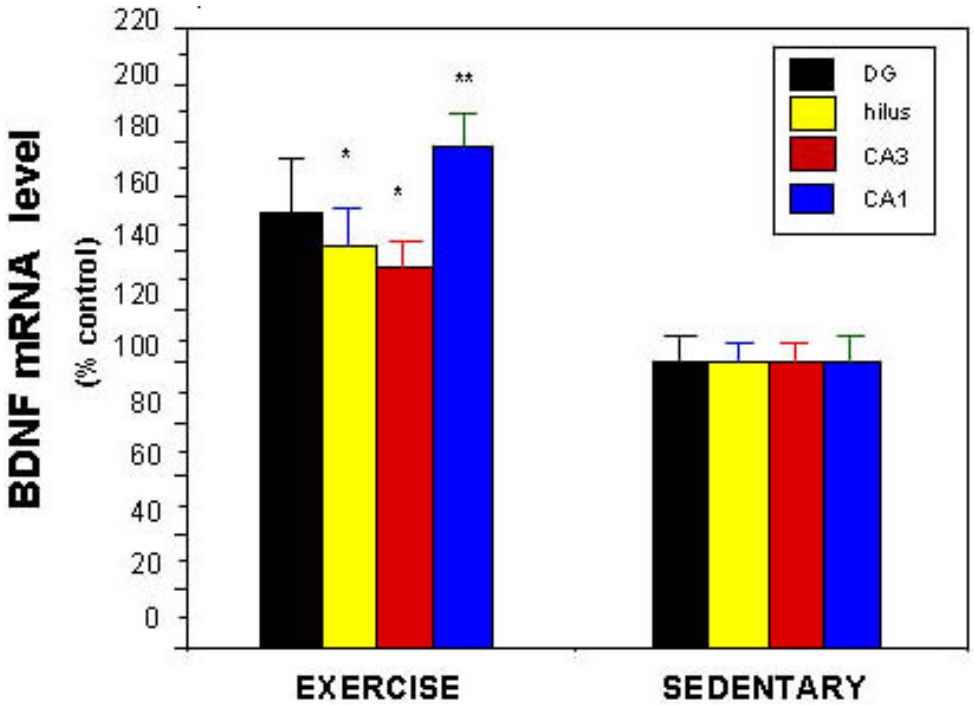
BDNF is a Synaptic Modulator

- Is BDNF induced by exercise and where in brain?
- How much exercise?

Exercise increases BDNF mRNA

HIPPOCAMPUS:

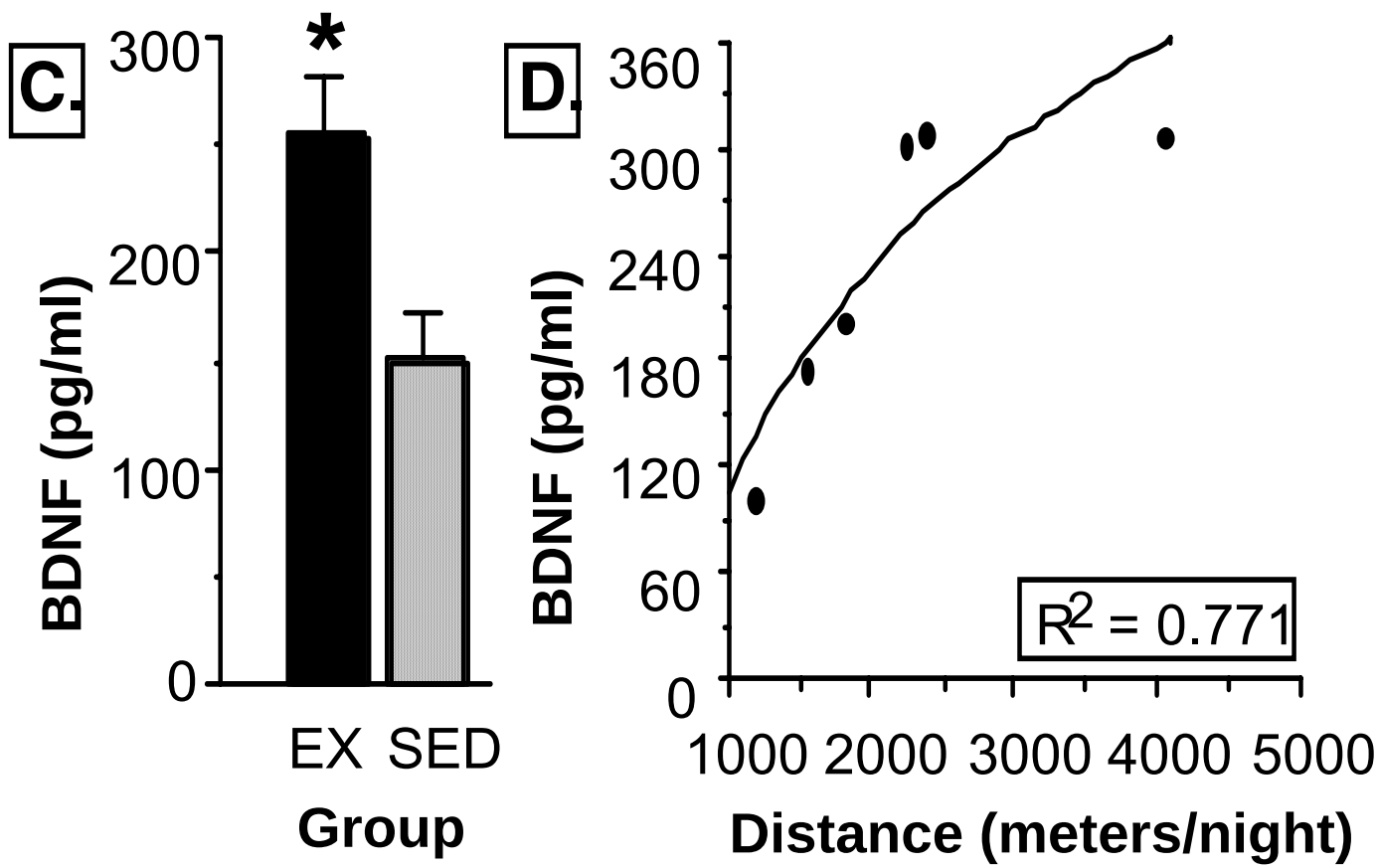




Rats: 1 week exercise (male sprague-dawley, 3 months)

Berchtold et al., 2002

Exercise increases BDNF protein



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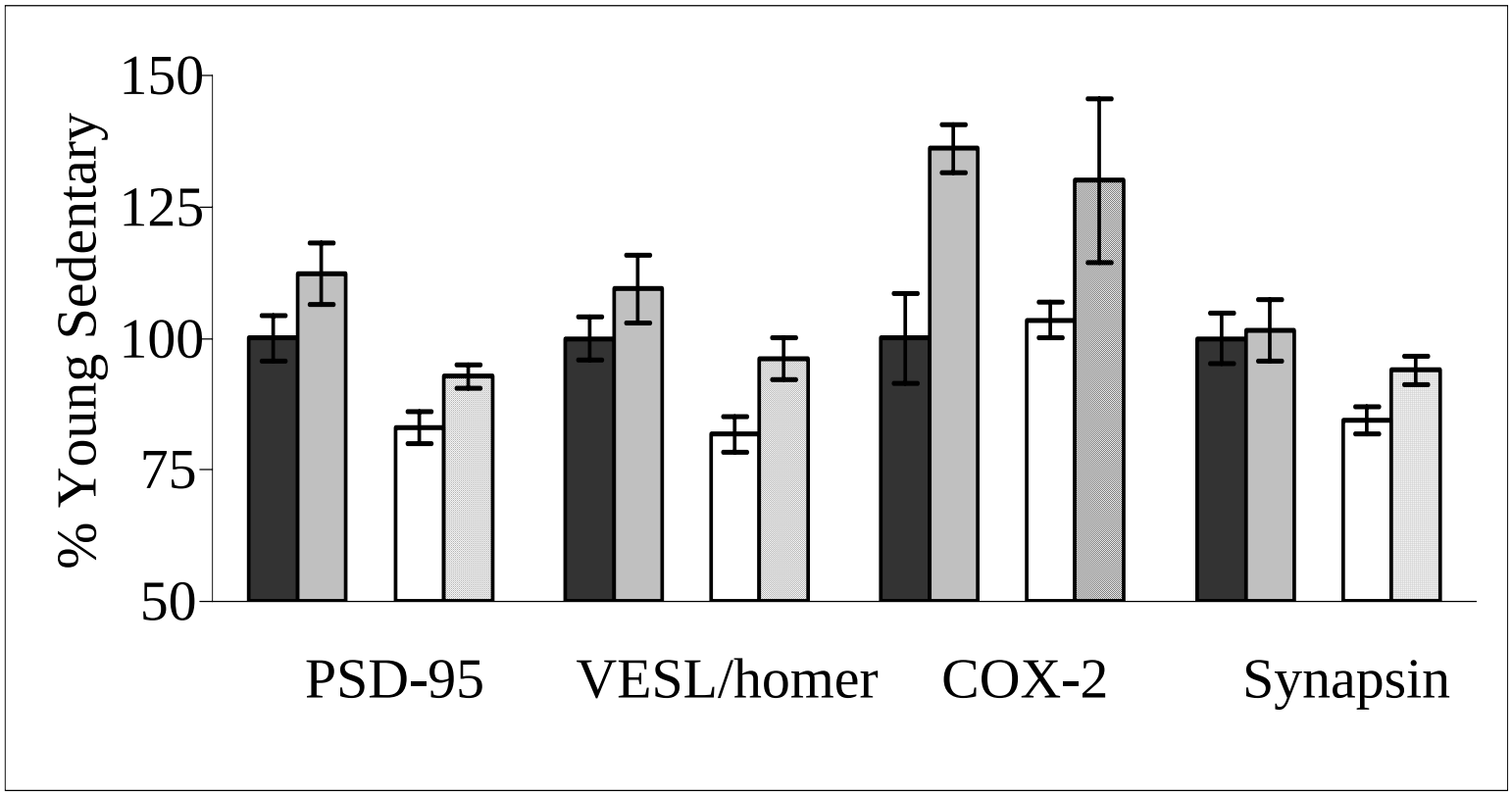
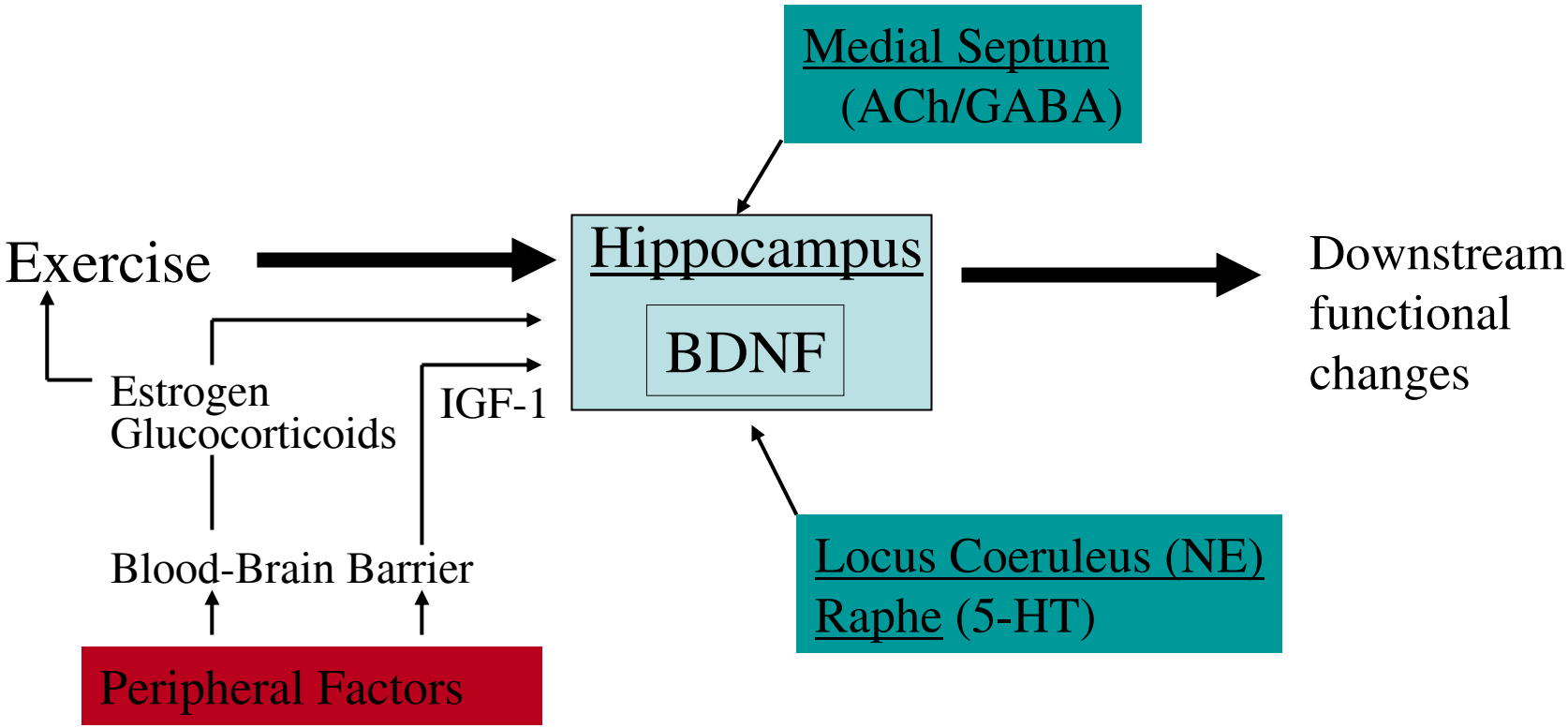
  - » Slice culture: BDNF increases NARP protein
- COX-2: traditionally known for immune function
  Role in plasticity: localized to dendrites
  - » Slice culture: BDNF increases COX-2 protein

Exercise “restores” some of the age-related losses in synaptic proteins



CNS and Peripheral Factors Interact with Exercise to Regulate BDNF



Cotman and Berchtold (2002), TINS

Practical Questions

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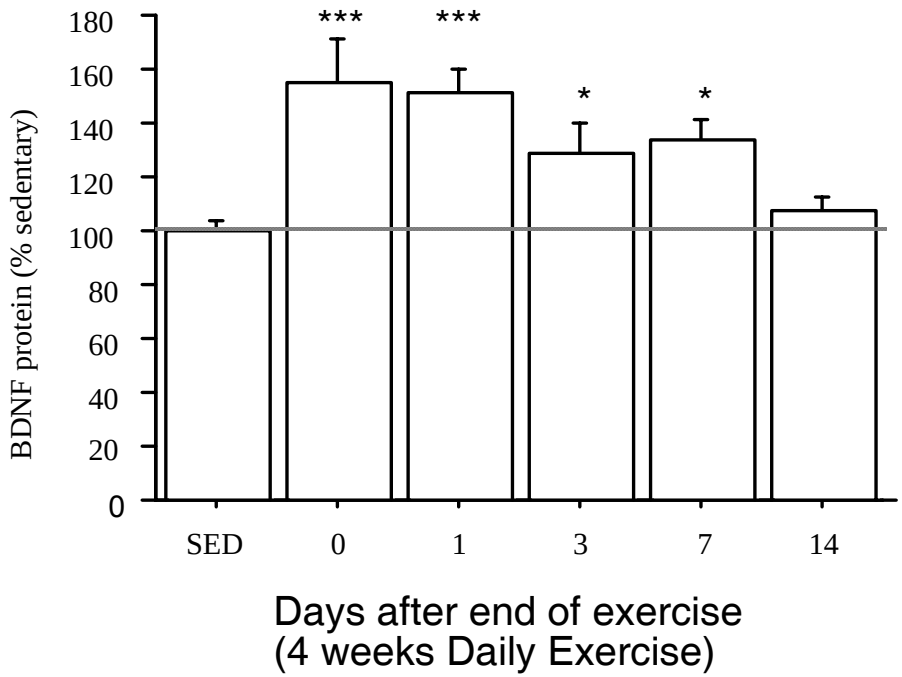
- How frequent is necessary
- Can the increase be recovered rapidly if exercise is stopped for a peroid?

BDNF Protein Stability

After Exercise Ends

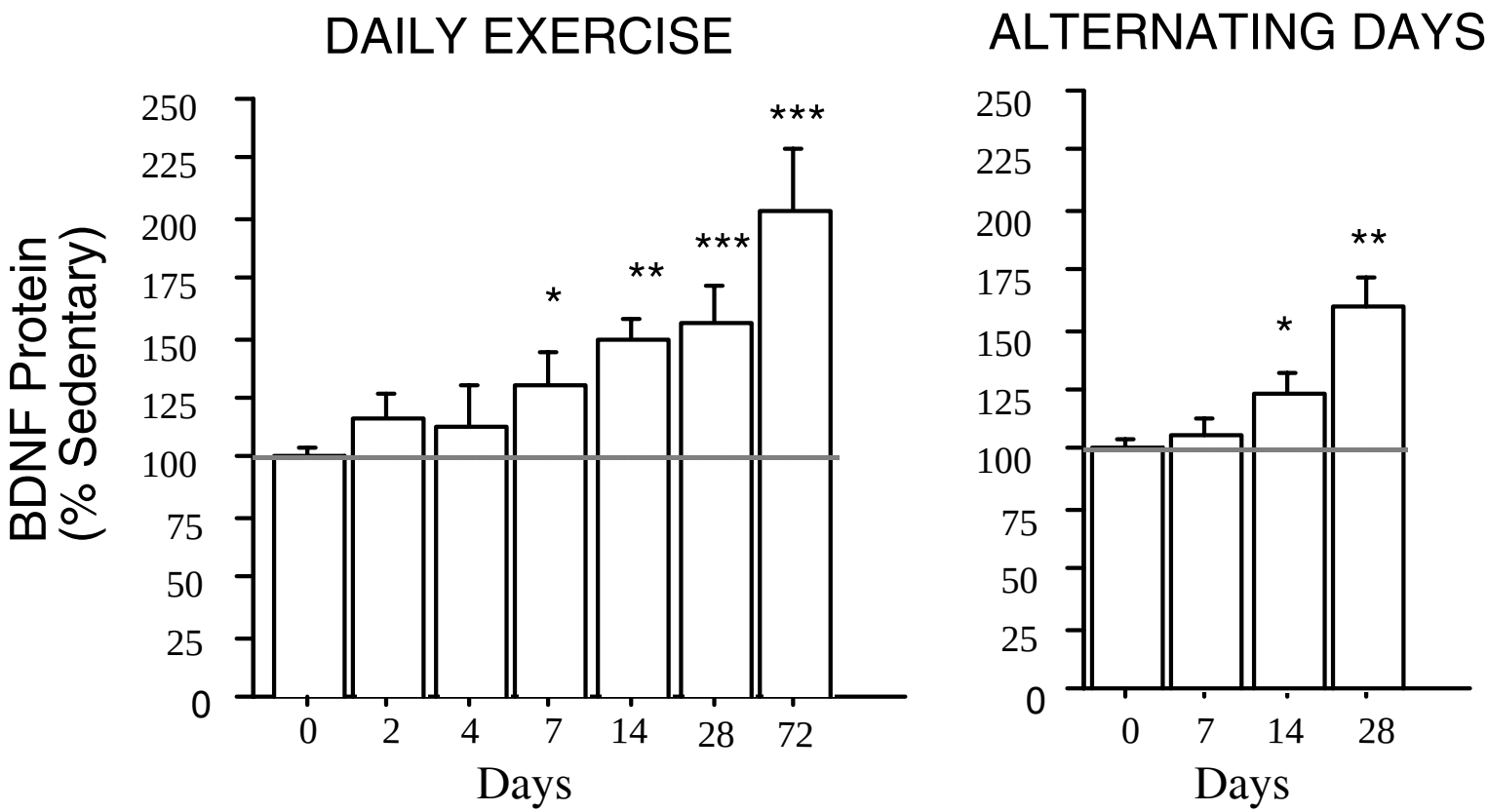
Paradigm:

- 4 weeks daily voluntary exercise
- Day 0 - end of exercise period,
  - wheels locked
- Sacrifice on days 0,1,3,7,14 after end of exercise
- Protein levels assessed



Berchtold, et al., submitted

Time course of BDNF Protein Induction



Berchtold, et al., submitted

Is there a molecular memory for exercise?

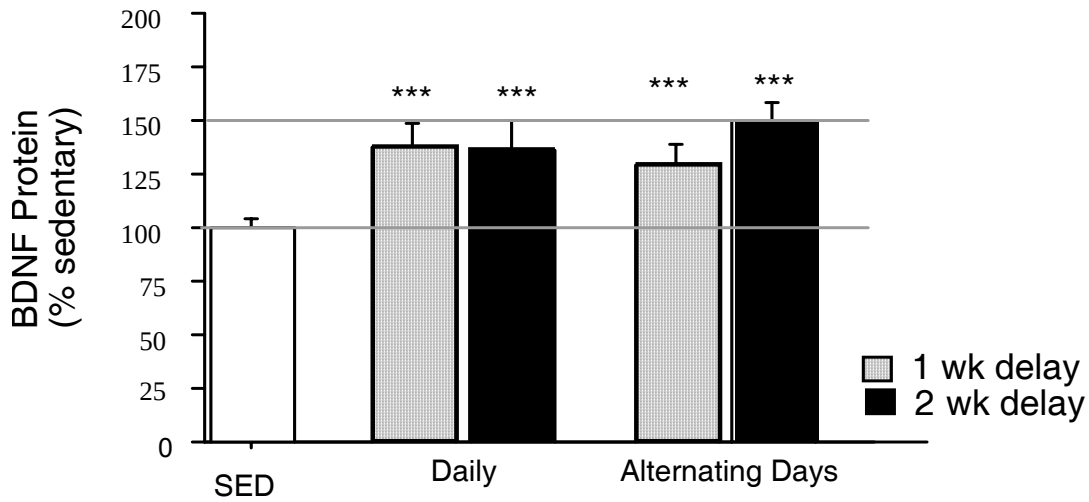
- Many of the gene changes including CREB are linked to learning and memory
- Is the experience of exercise encoded so to allow the brain to learn to respond?

Thus, if so exercise may prime the brain to respond to experiences, and induce a “state of readiness”.

Once exercise stops is the induction stored in molecular memory?!

Paradigm:

- 14 days of exercise:
  - Daily (during 2 weeks)
  - Alternating (during 4 weeks)
- Wheels locked:
  - 1 week, 2 weeks
- Second short run period (2 days)
- **Note: 2 days exercise alone is not sufficient to increase BDNF**

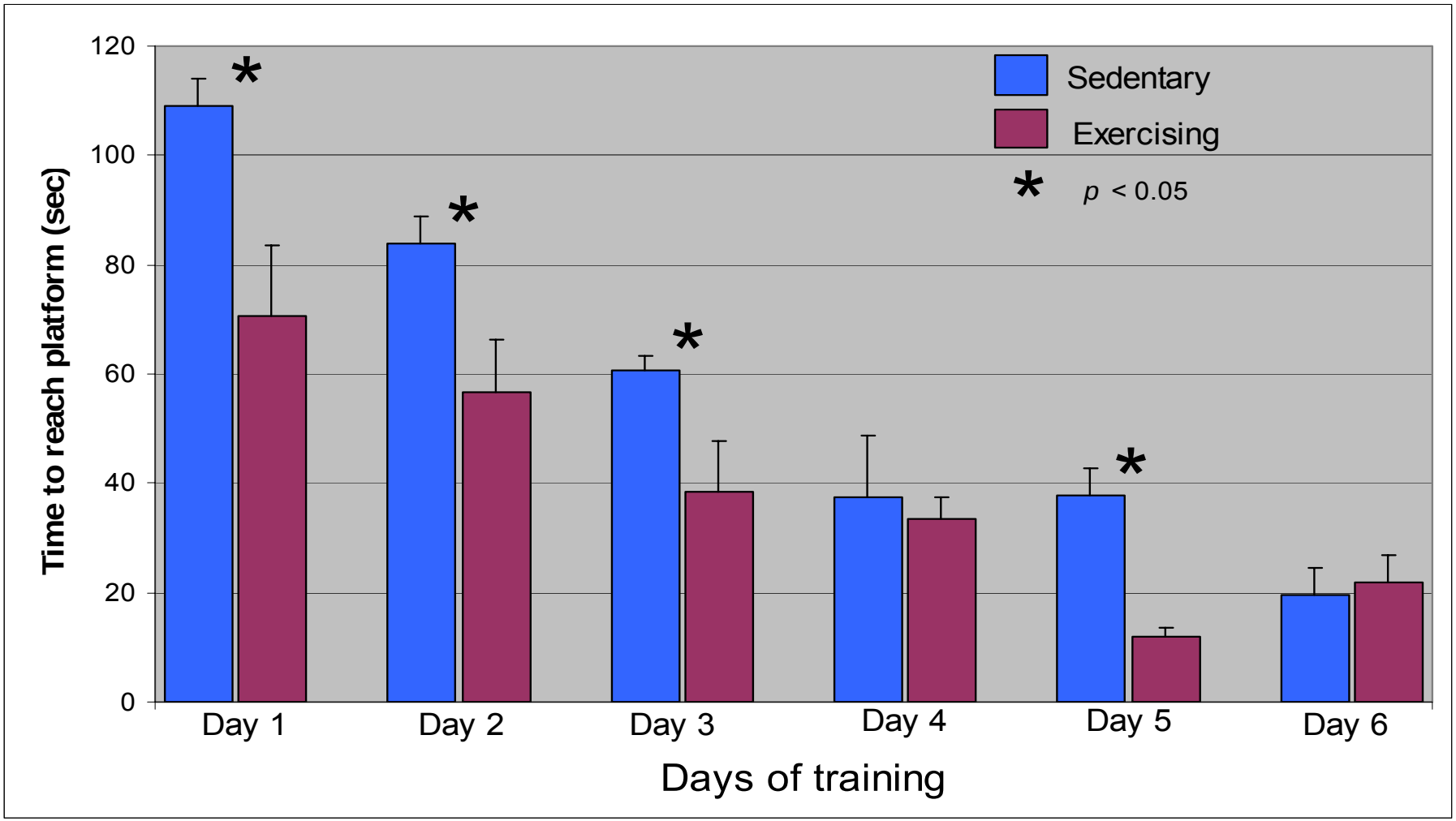


- Prior Exercise Primes subsequent BDNF Responsiveness
- Priming effect endures at least 2 weeks
- Equivalent Secondary Responsiveness if prior exercise is Daily Regime or Alternating Days of Exercise

So … What is the functional significance of brain changes induced by exercise?

- Learning?
- Stress relief?

Exercise Enhances Learning in the Morris Water Maze



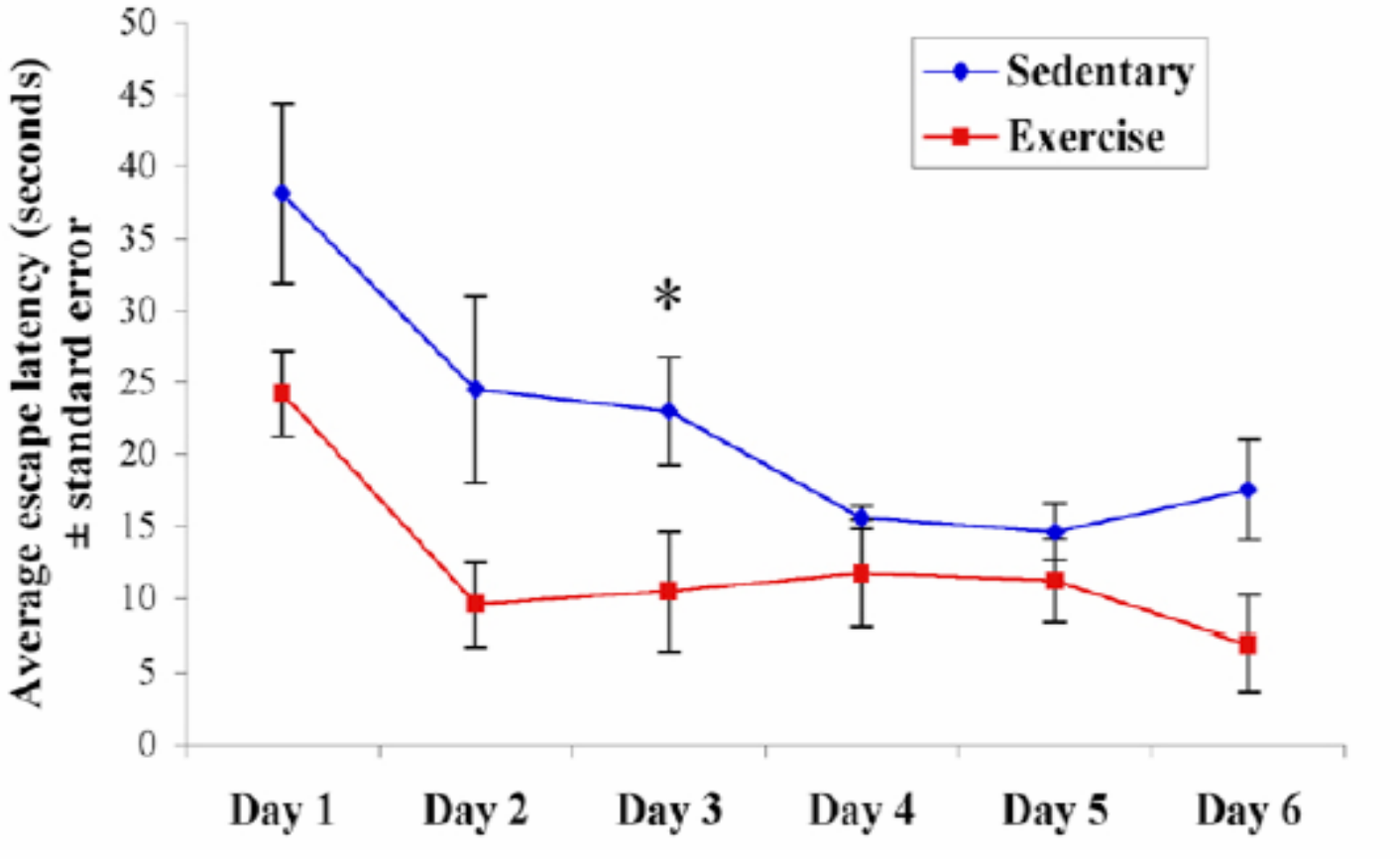
Is exercise an effective intervention in AD transgenic models ?

- Will voluntary running improve learning and memory?
- Reduce β-amyloid in the brain?
- Stimulate neurogenesis?

Voluntary Exercise Paradigm

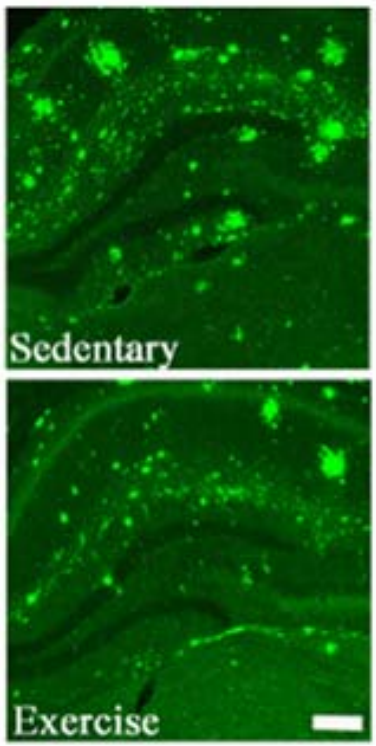
- Utilized TgCRND8 mouse model
- Voluntary access to running wheels (animals run ~3 miles/day)
- Short-term running
  - start at 6 weeks of age
  - sacrifice four weeks later
- Long-term running
  - start at 6 weeks of age
  - sacrifice 5 months later

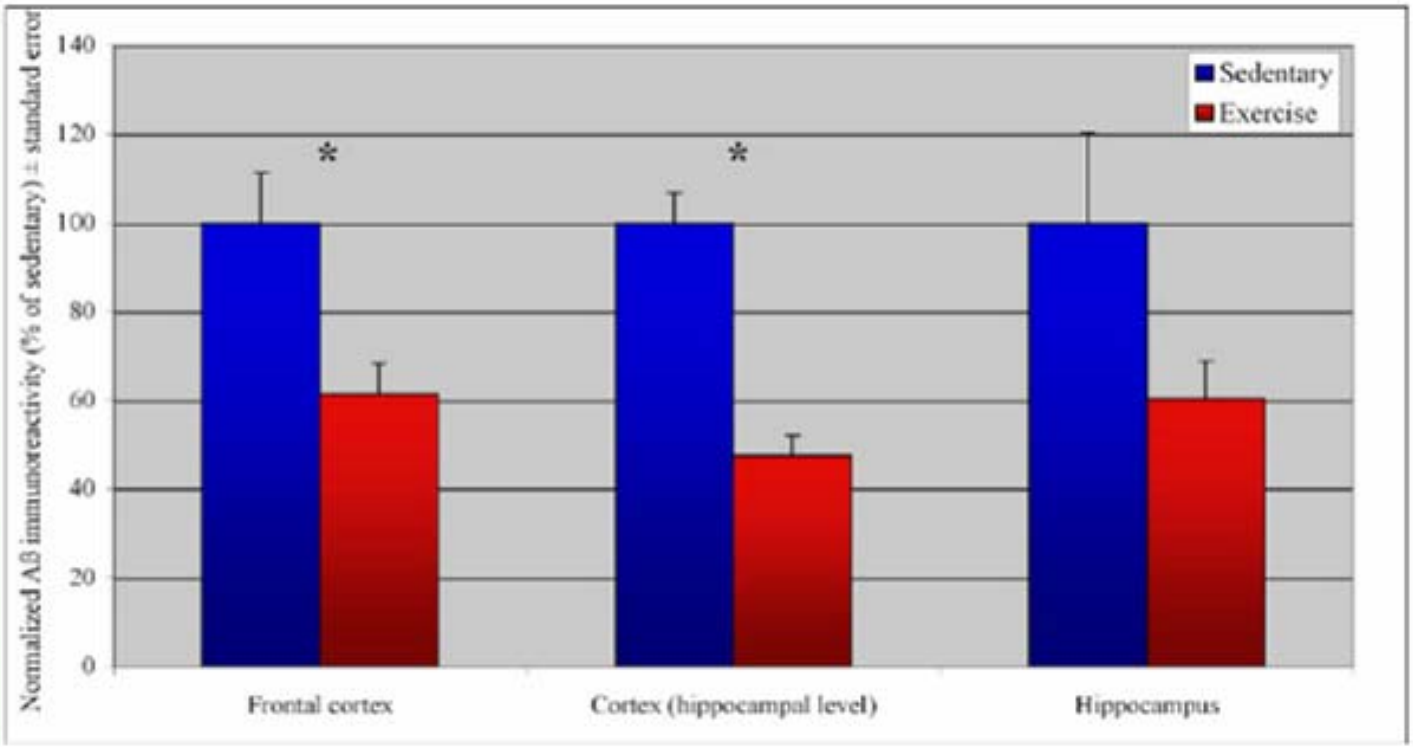
Long-term running enhances the rate of learning in TgCRND8 animals



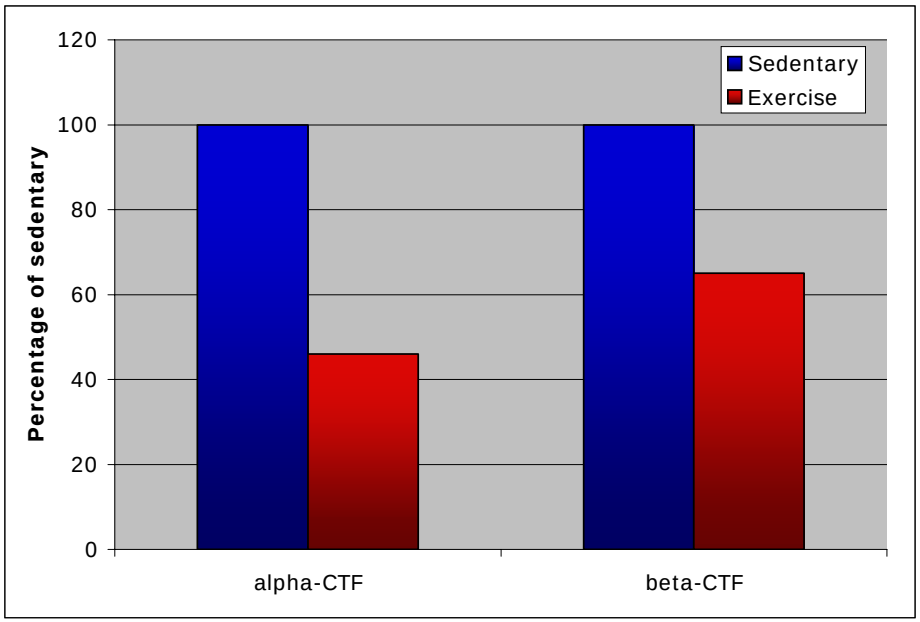
Long-term running reduces ß-amyloid load in TgCRND8 animals

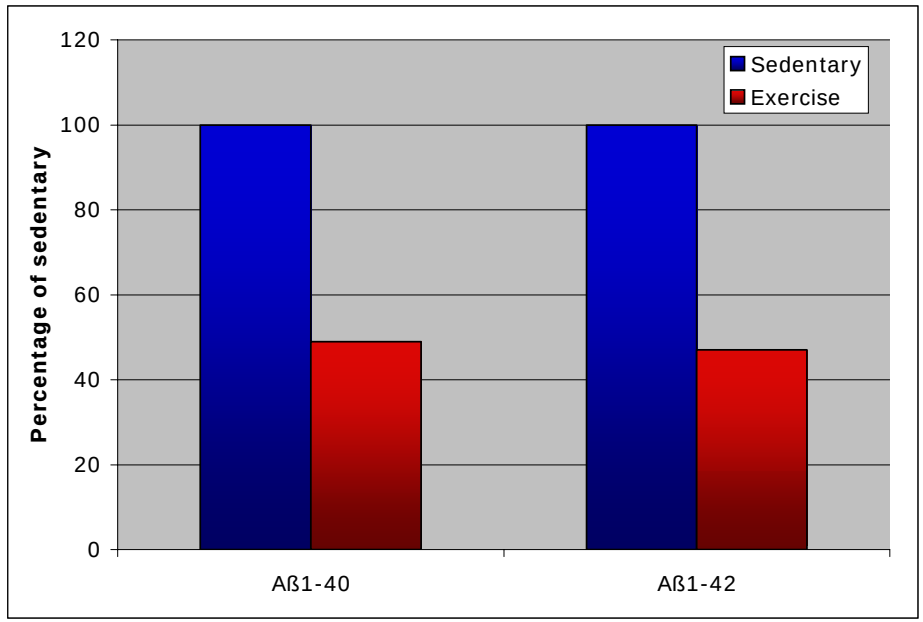
(by immunohistochemistry)

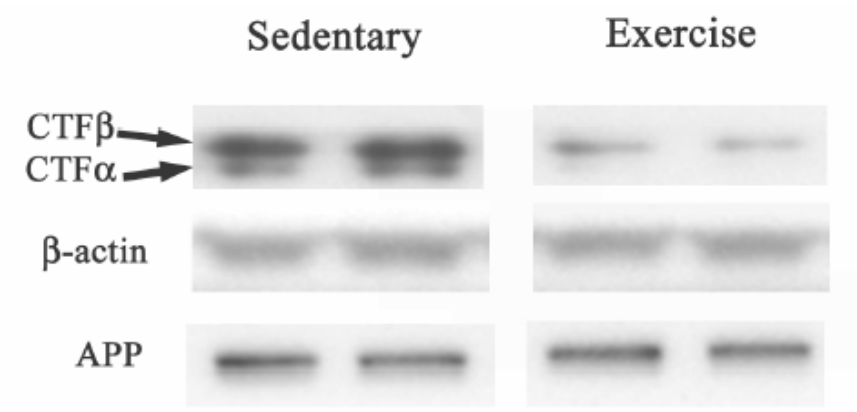




Short-term running mediates APP processing





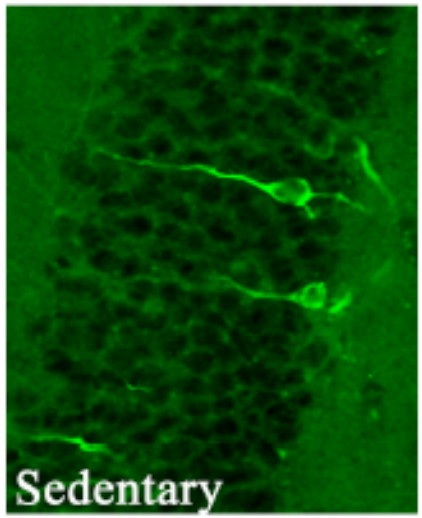


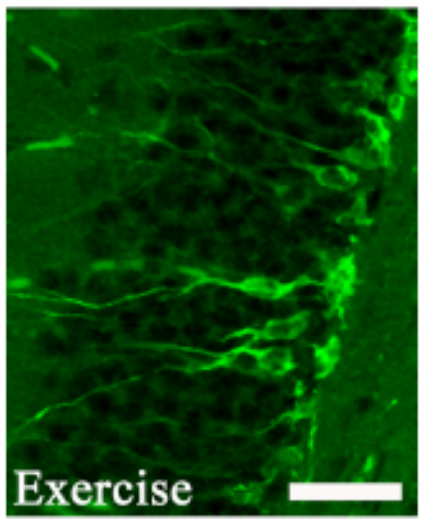
- no effect on total APP
- no effect on secretase activity (α, β, γ)
- no effect on neprilysin or IDE

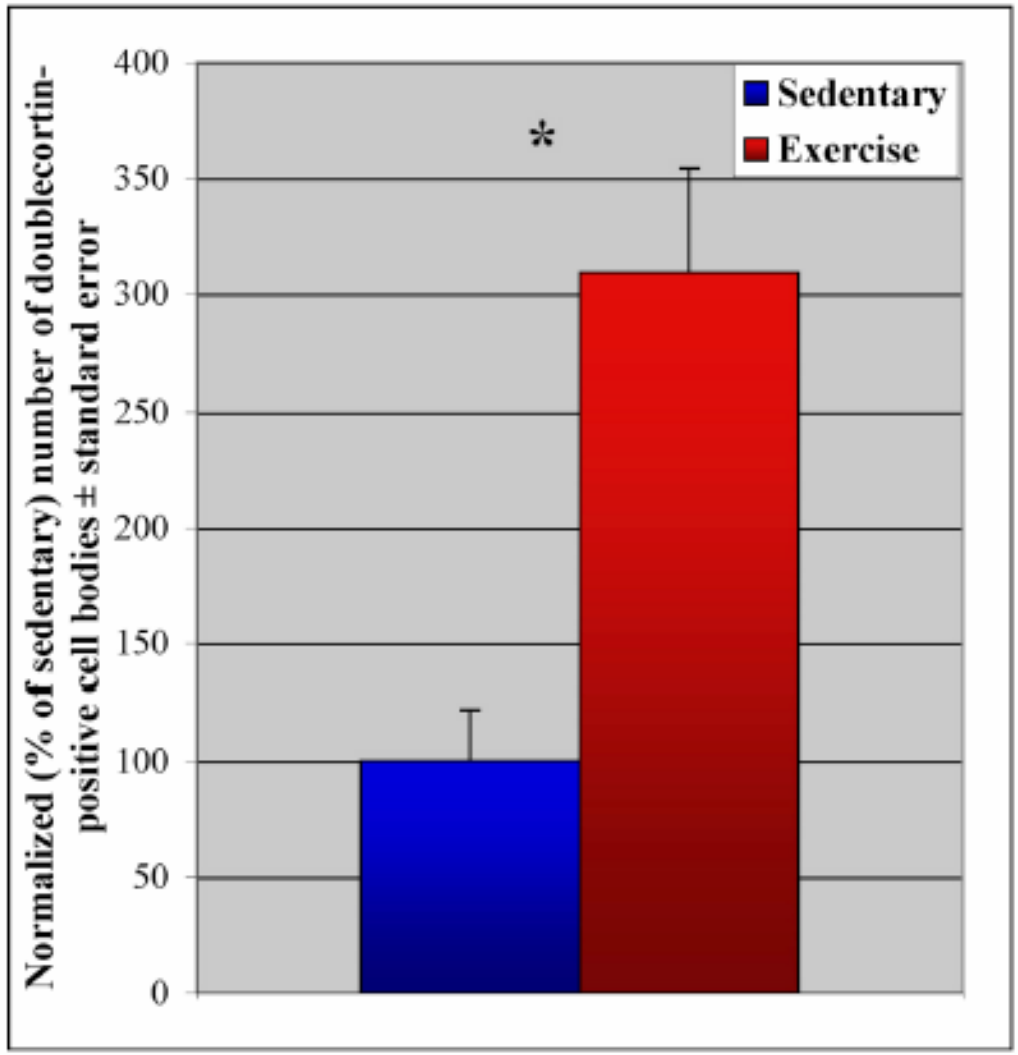
Why is learning and memory improved?

- Hypothesis – Neurogenesis?
- Hypothesis – Aβ may impair CREB and Elk transcriptional activity essential for learning and memory, e.g., induced by BDNF

Long-term running enhances neurogenesis in TgCRND8 animals





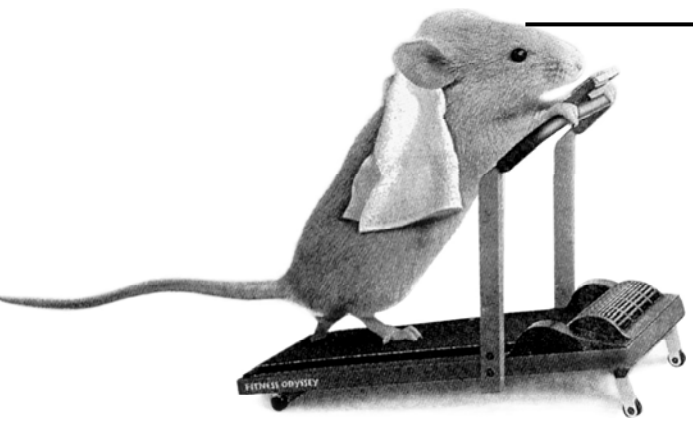


Recent clinical/ epidemiological findings

- Exercise and intellectual activities in mid life delay AD onset (Friedland, 2001)
- TV is associated with an increased risk of AD, 1.3X risk/hr of TV/day (Friedland, 2005)
- Exercise increases brain volume in select areas and larger brains are associated with those most fit (Kramer, 2004,2005)
- Women who get the most exercise show less cognitive decline (Yaffe, 2005;Grodstein, 2004)
- Those engaged in 4 or more physical activities have half the risk for AD, but mainly for ApoE4 carriers (Lyketsos, 2005)

Exercise

Exercise → **Functional changes:**



→ **?** →

-Increase BDNF
-synaptic plasticity
-Increased neuron number
-Improve learning