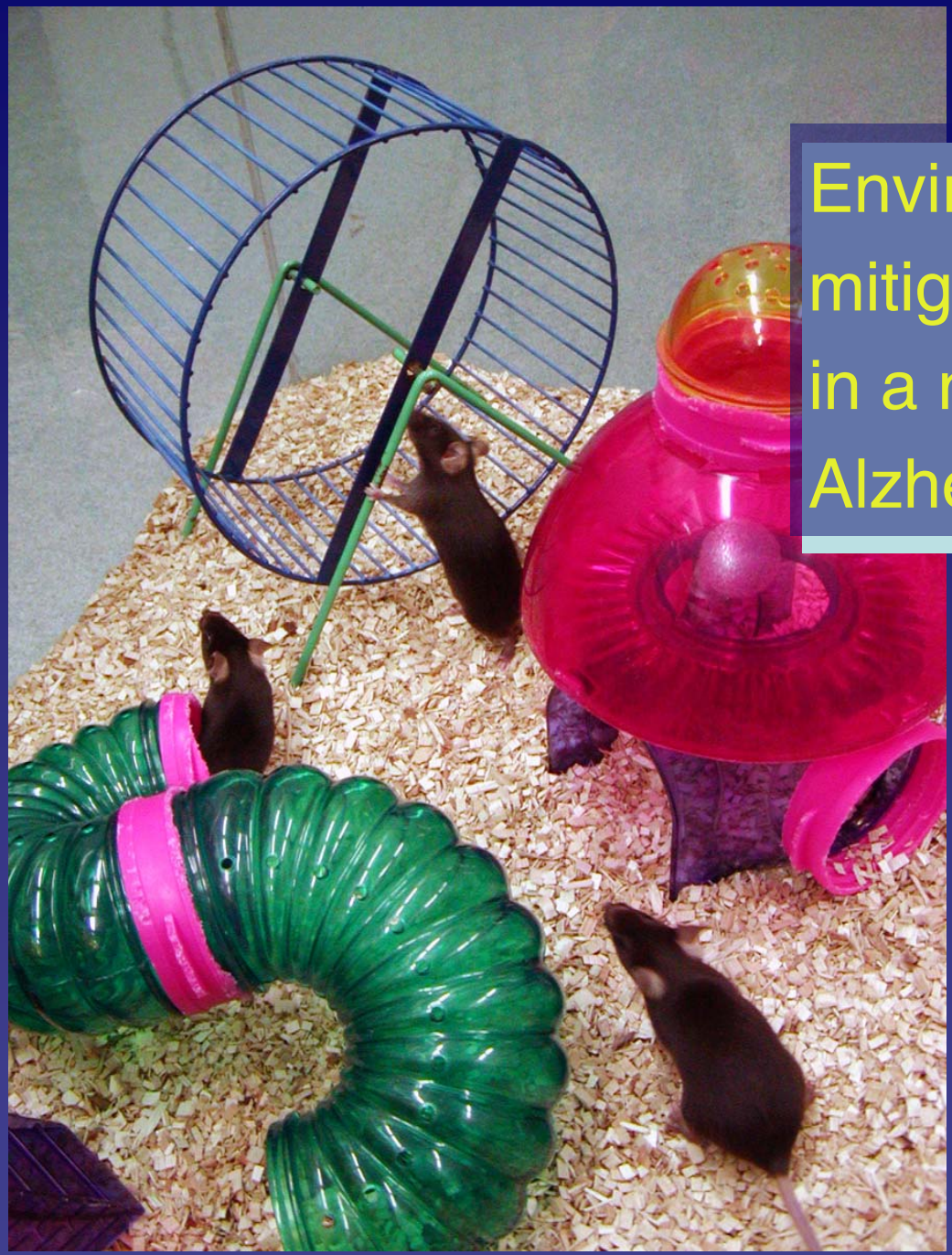

Environmental enrichment mitigates cognitive deficits in a mouse model for Alzheimer's disease

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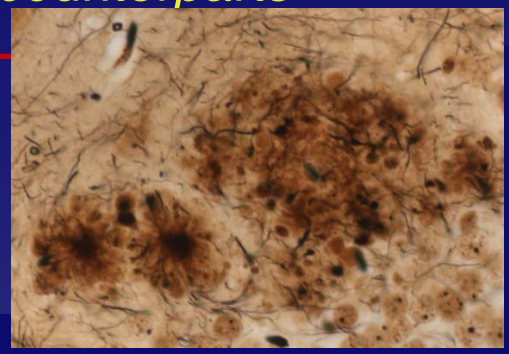
Standard housing

Environmental enrichment

APPswe x PS1dE9 transgenic mice

and their single transgenic counterparts



APPswe x PS1dE9:

- Early-onset amyloid lesions
- Age-associated cognitive decline

APPswe:

- Produces less Aβ than APPswe x PS1dE9
- Very late-onset amyloid plaques and cognitive decline

PS1dE9:

- Augments Aβ production in APPswe mice, but little effect by itself

Differential housing

Differential housing

Differential housing

Experimental design

- Age and gender matched cohorts, congenic C57BL/6J
- 32-40 mice per condition (EE or control)
- 4 genotypes: APPswe x PS1dE9
  APPswe
  PS1dE9
  NTg

Multi-dimensional behavioral battery

Edge retreat visual acuity test

Straight swim control for motor skills

Standard Morris Water Maze
test of long-term reference memory

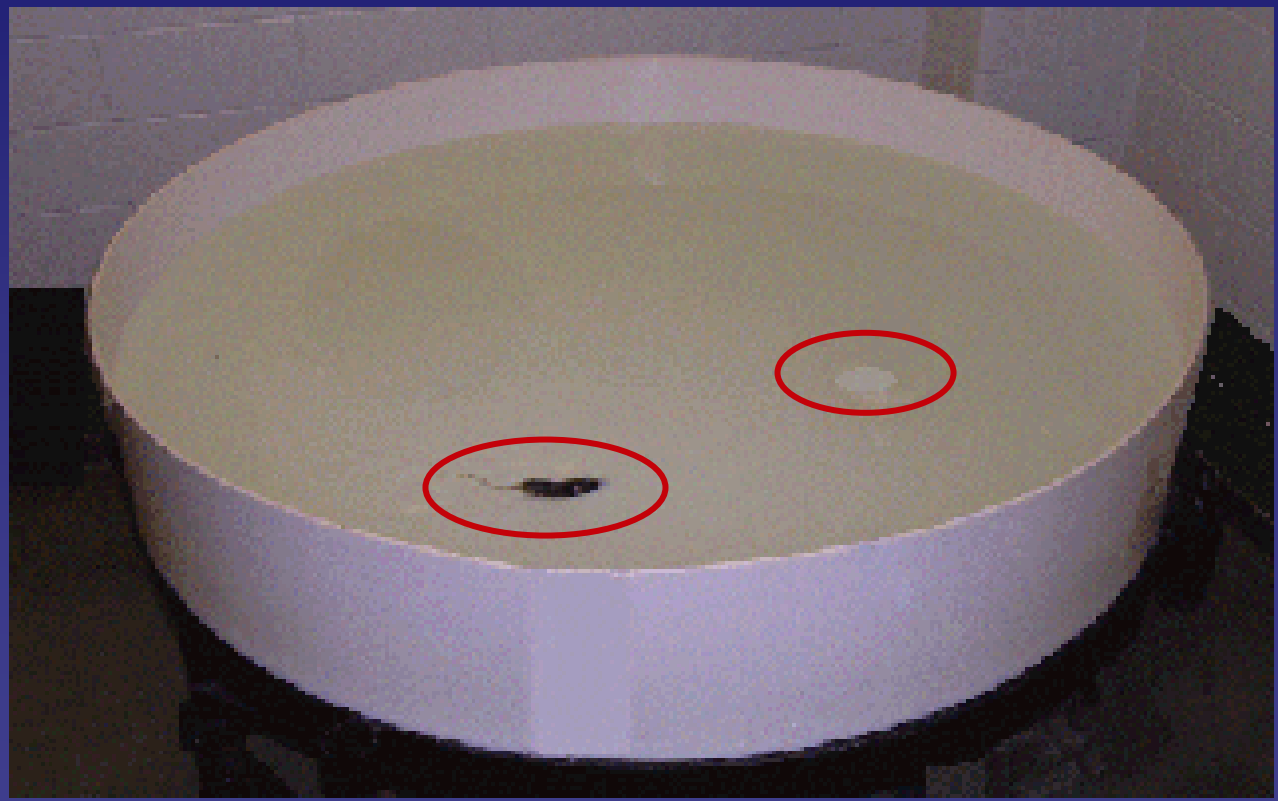
Repeated Reversal Water Maze
test of episodic-like memory

Six Arm Radial Water Maze
test of episodic-like and working memory

Visible Platform Water Maze
final control for visual acuity and motor skills

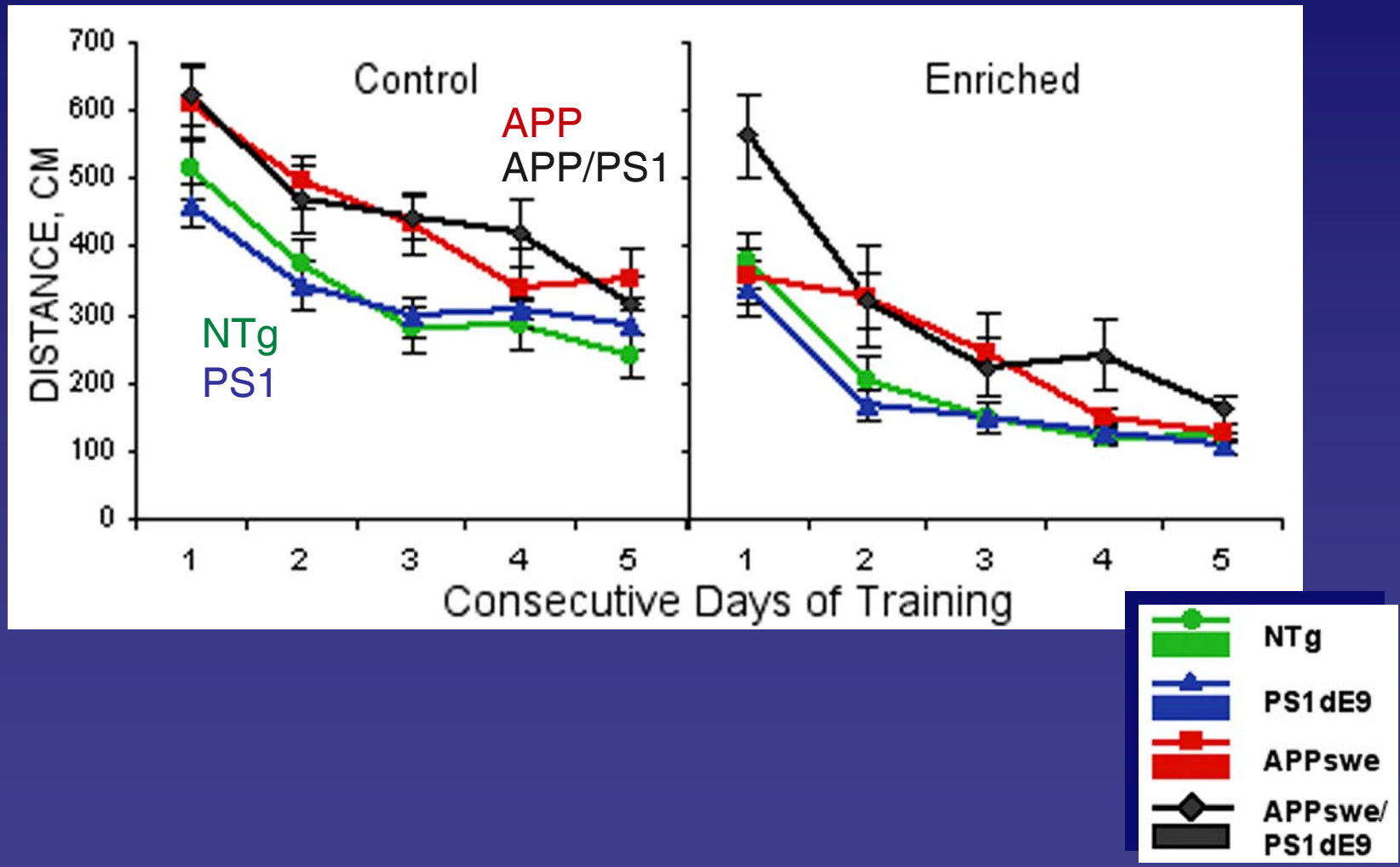
Standard Morris Water Maze

5 days, same platform location
10 training trials and 2 probe tests per day

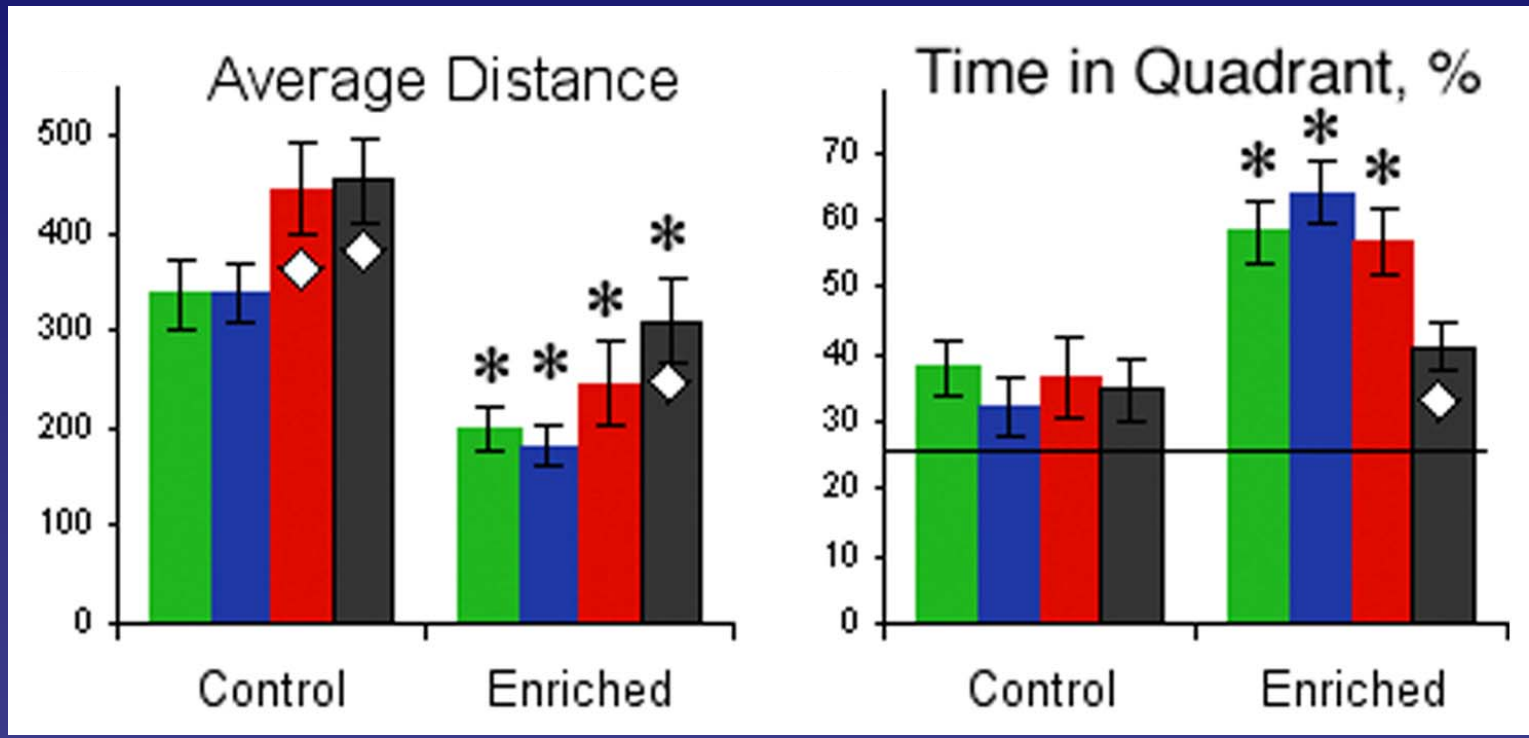


Morris, 1984 J Neurosci Meth 11:47
Frick et al. 1995 Neurobiol Aging16:149

Standard Morris Water Maze

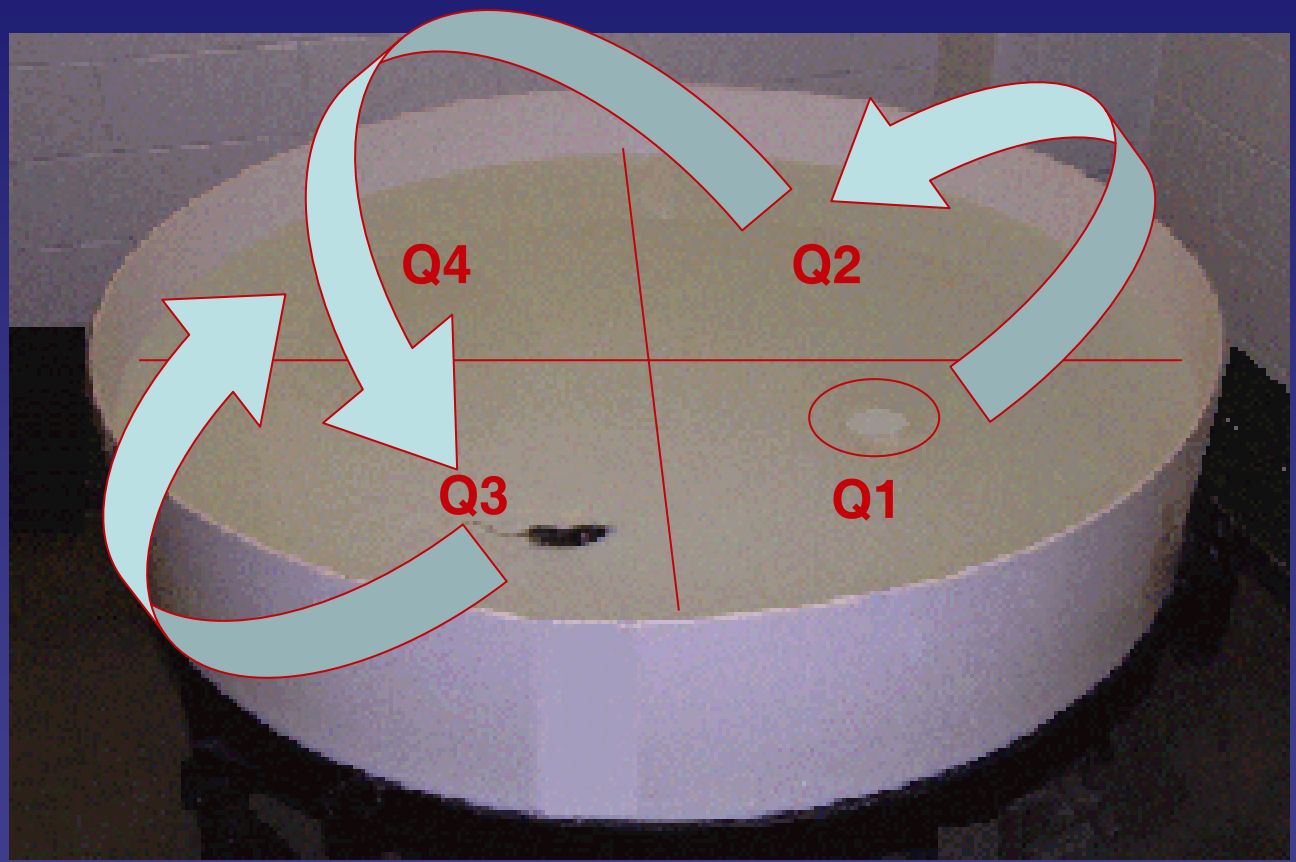


Standard Morris Water Maze



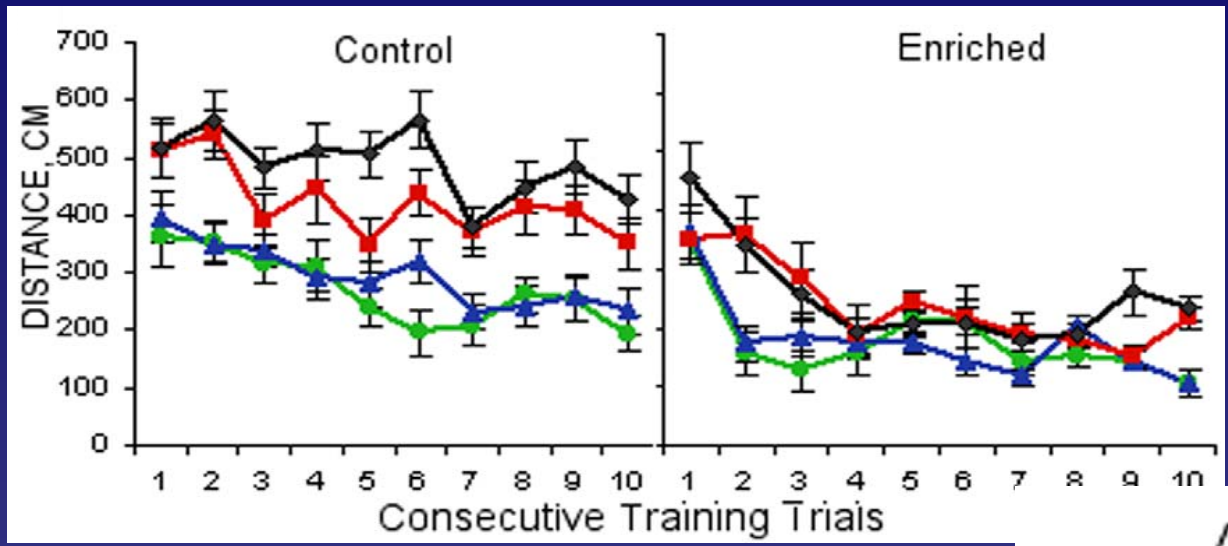
Repeated Reversal Water Maze

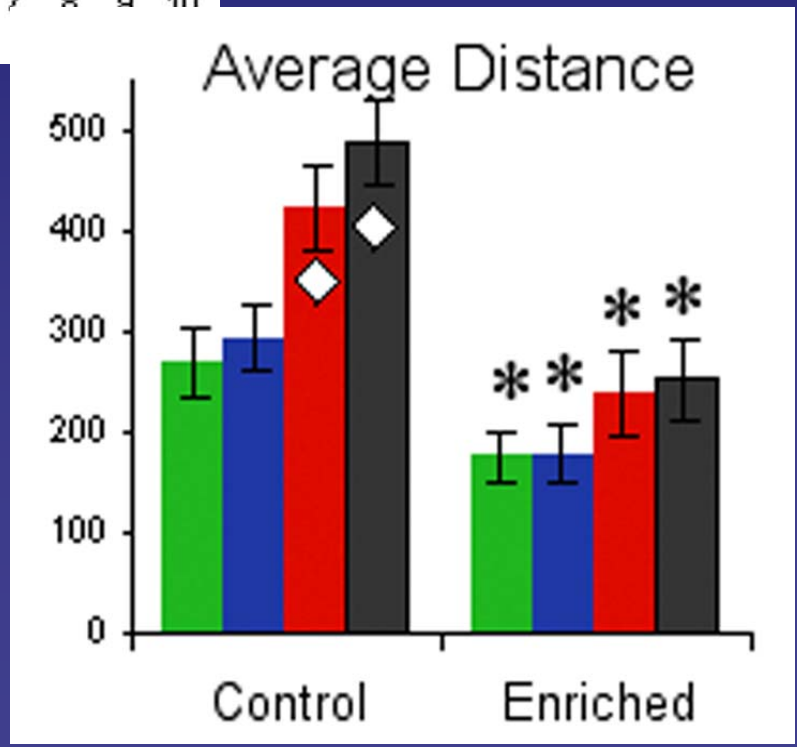
3 days, platform location moved each day
10 training trials and 2 probe tests per day



Chen et al. 2000 Nature 408:975
Morris 2001 Philos Trans Lond 356:1453

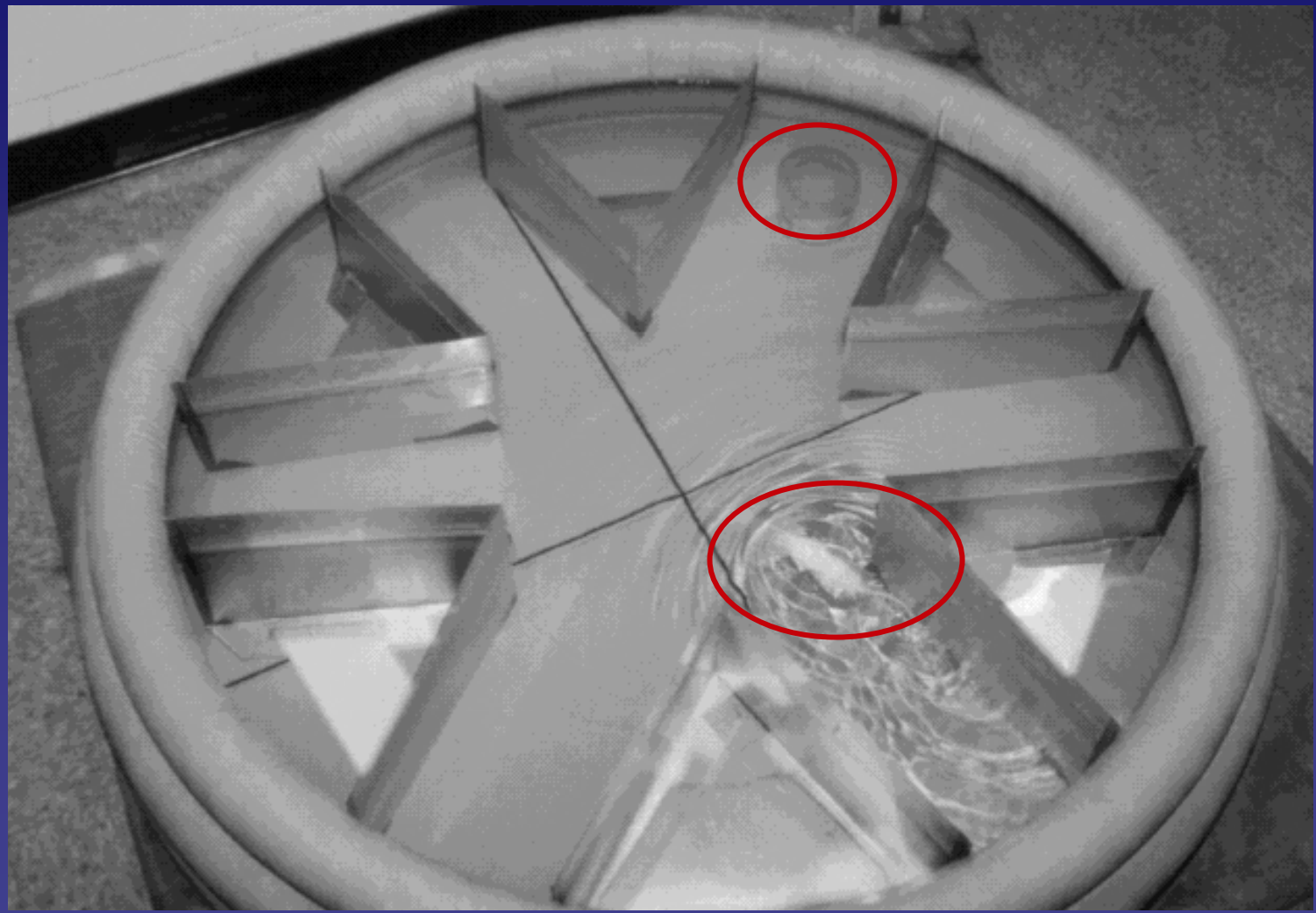
Repeated Reversal Water Maze





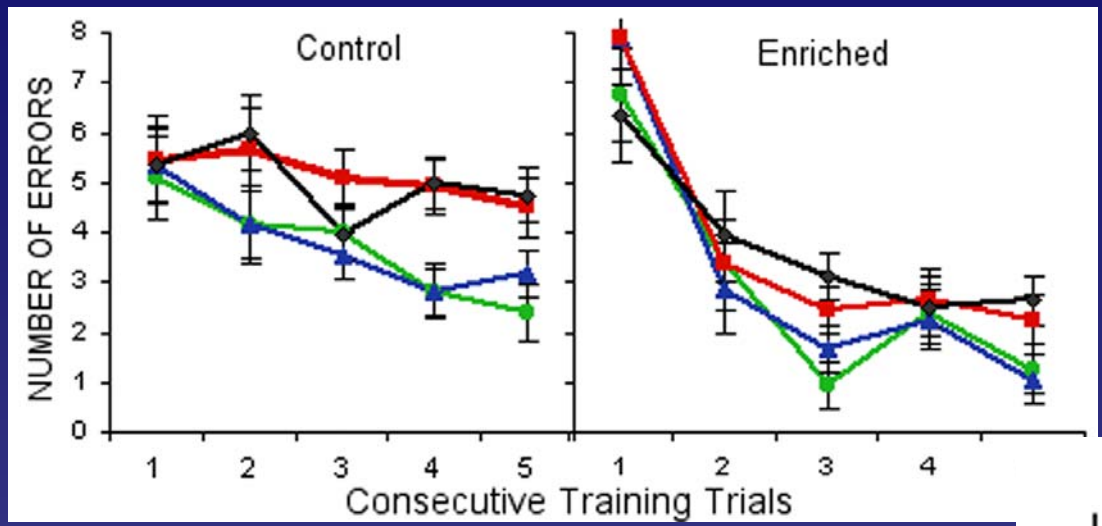
Six Arm Radial Water Maze

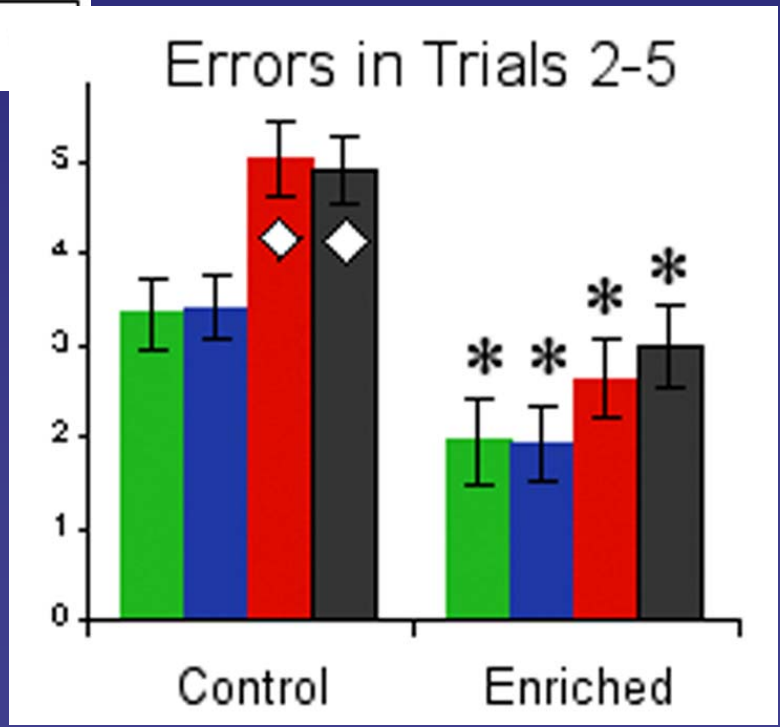
5 days, platform location moved each day
5 training trials and 1 probe test per day



Morgan et al. 2000 Nature 408:982

Six Arm Radial Water Maze





So behavior improved across all tests examined… what about pathology?

Enriched mice

- swim less distance to reach the platform,
- readjust their learning strategy more quickly,
- and make fewer maze errors

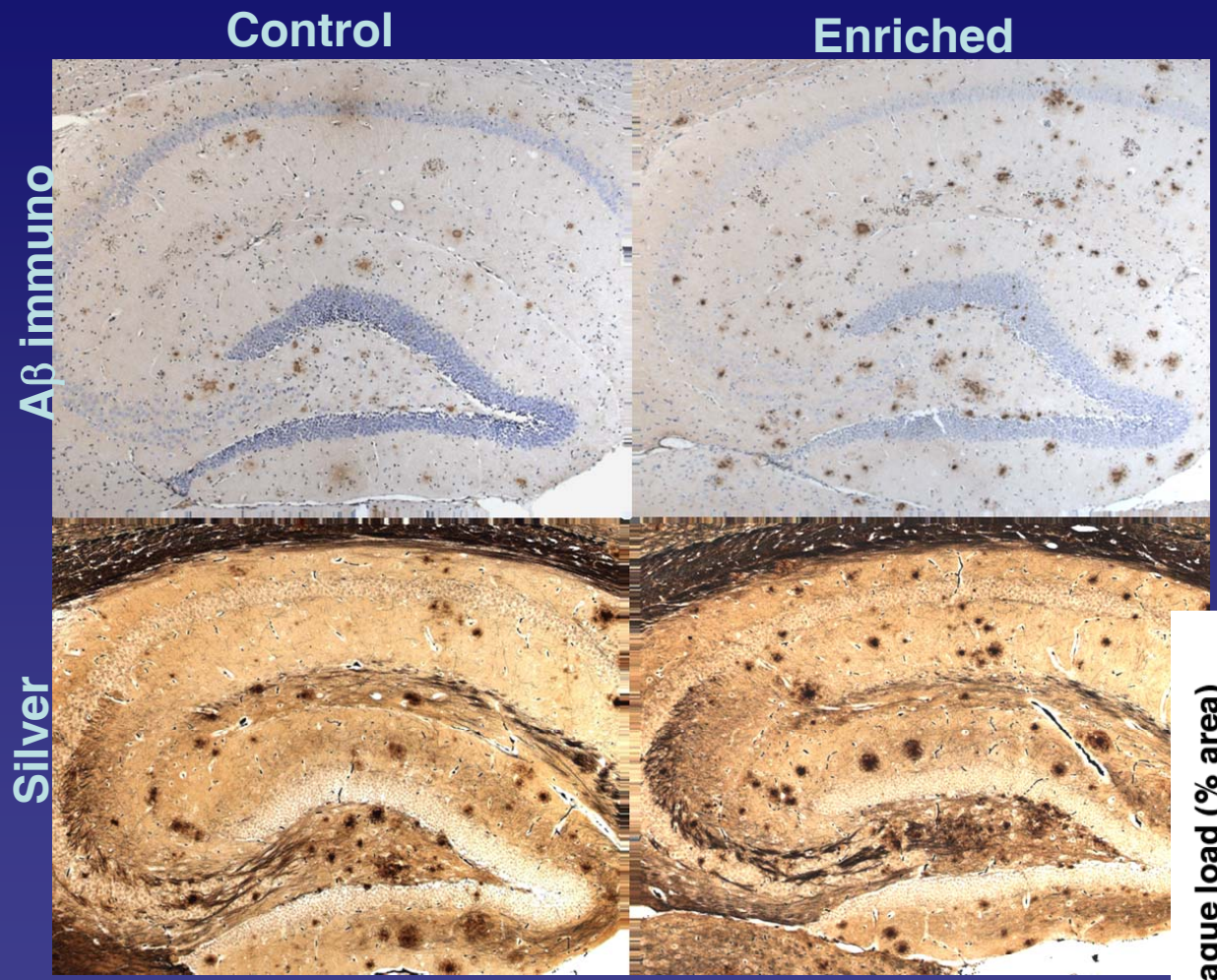
than standard-housed animals.

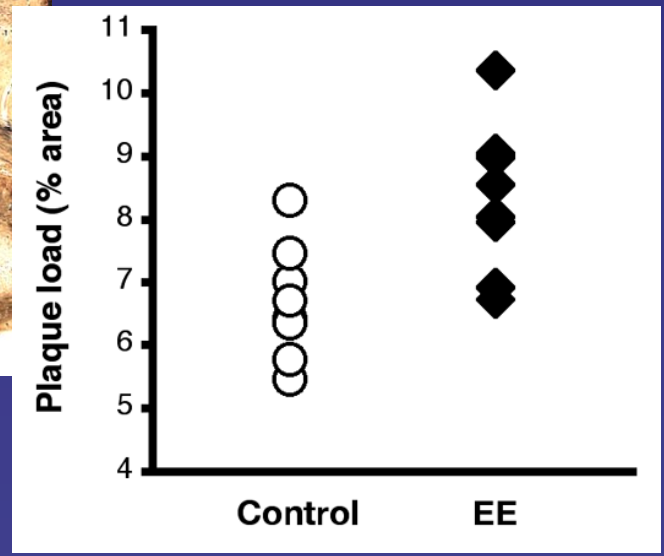
How do they do it?

How have they staved off cognitive decline associated with APP/Aβ?
Do they have less pathology? Fewer plaques? Less Aβ?

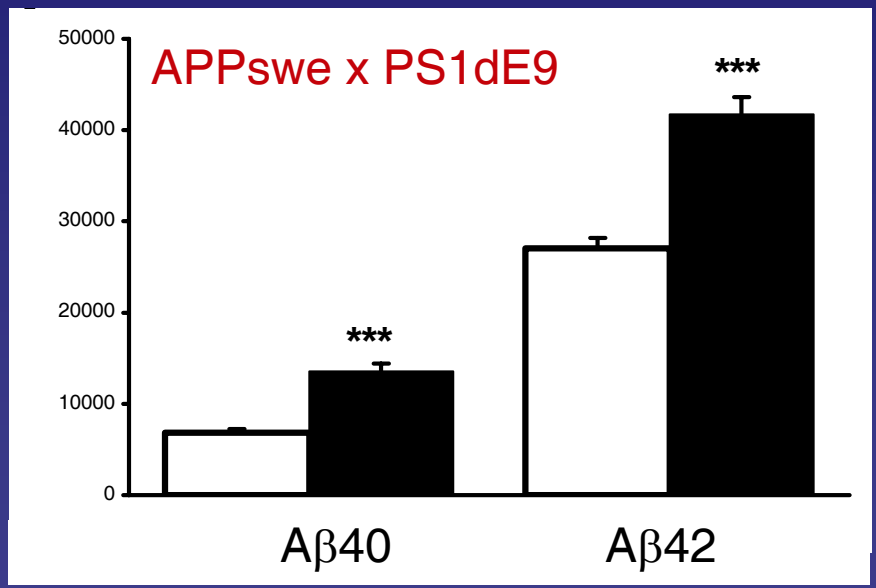
Previous work suggests otherwise…

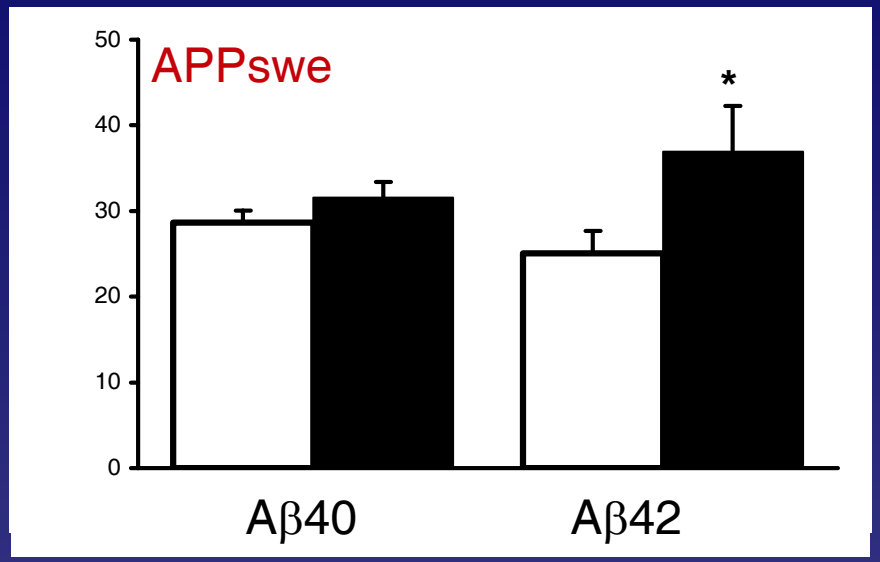
Enrichment *increases* amyloid load

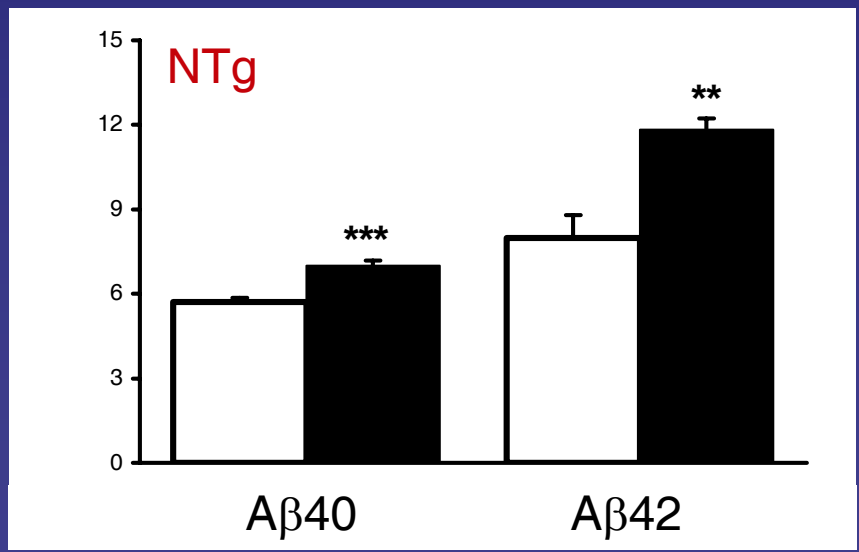




Enrichment *elevates* both endogenous and transgenic Aβ







How to reconcile increased Aβ/amyloid load with improved cognitive performance?

Cognitive reserve

Proposed to explain the protective effects of education, occupation, and leisure activities against dementia

Suggests that physical changes such as increased neuronal connectivity, or functional changes such as alternative retrieval strategies may allow the brain to withstand greater insult before succumbing to dementia

Other benefits of enrichment, including greater synaptic density, stronger neuronal connectivity, and increased neuronal survival more than compensated for damage caused by extra Aβ

Other studies of AD mice and enrichment

Environmental enrichment improves cognition in aged Alzheimer's transgenic mice despite stable β-amyloid deposition

NeuroReport 15:1751–1754 © 2004

Gary W. Arendash,[1,2,CA] Marcos F. Garcia,[2] David A. Costa,[1,3] Jennifer R. Cracchiolo,[2] Inge M. Wefes[3] and H. Potter[1,3]

Environmental Enrichment Reduces Aβ Levels and Amyloid Deposition in Transgenic Mice

Cell, Vol. 120, 701–713, March 11, 2005,

Orly Lazarov,[1] John Robinson,[1] Ya-Ping Tang,[2] Ilana S. Hairston,[3] Zeljka Korade-Mirnics,[7] Virginia M.-Y. Lee,[4] Louis B. Hersh,[5] Robert M. Sapolsky,[3] Karoly Mirnics,[6,*] and Sangram S. Sisodia[1,*]

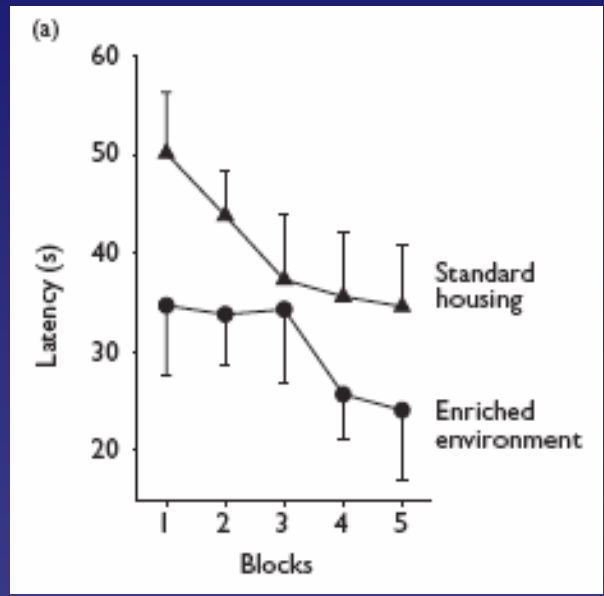
Environmental enrichment improves cognition in aged Alzheimer's transgenic mice despite stable β-amyloid deposition

Main finding: Behavioral improvement, no change in amyloid load

Nice features:

Continuous enriched housing plus
novel environment 3x/wk

Four behavioral tests: Morris water maze
Circular platform
Platform recognition
Radial arm water maze



Points of difference:

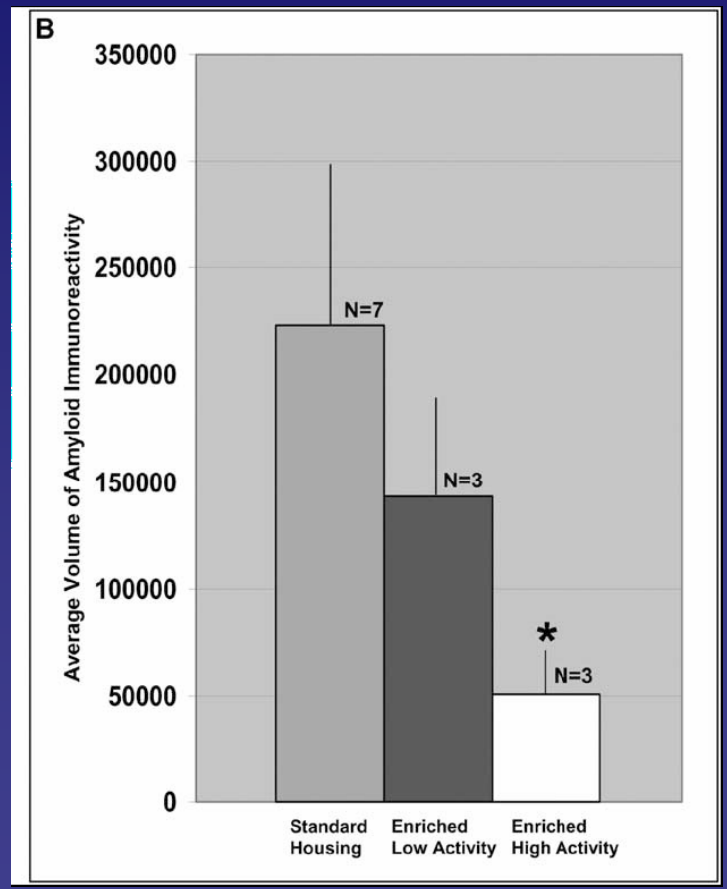
One genotype (APPswe)
Hybrid C57/SJL/SW/B6D2 background
Mice were older: EE from 16-22 months, cognitive testing at 20-22 months
Gender not stated

Main limitation:

Small cohort: n=4 control, n=5 EE but 2 died…
Required "higher level statistical analyses" to identify significant changes

Environmental Enrichment Reduces Aβ Levels and Amyloid Deposition in Transgenic Mice

Main finding: reduced Aβ levels in enriched mice; greatest benefit in mice with high activity levels



Nice features:

Examined mechanism of change by looking at Aβ synthesis and degradation

Find increased Nep activity in EE cohort

Points of difference:

One genotype (APPswexPS1dE9)

Unstated background

Male animals

Intermittent enrichment, emphasis on exercise

Main limitation:

Small cohort: n=7 control, n=6 EE

Enrichment or exercise as main feature of experiment?

What to make of it all?

Differences likely due to variations in experimental

Enrichment comes in many flavors: Social cohort
Novelty
Exercise

Response to enrichment may also vary: Gender
Age
Genotype

Nonetheless, ***points of commonality*** **emerge:**

- Environment modifies Aβ currency
  - External effect on brain biochemistry (no drugs needed!!)
- Enrichment improves behavior
  - Preventative and palliative

Acknowledgements

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David Borchelt

Guilian Xu
Vicky Gonzales
Hilda Slunt

Linda Younkin
Steve Younkin
Daniel Fadale

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