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

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Standard housing
Environmental enrichment

Behavior
Neurogenesis
Synaptic density
Dendritic arborization
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

- 3-4 mice per cage
- 600 cm² total floor space
- No toys or exercise wheels
Differential housing

- 16 mice per cage
- 10,000 cm² total floor space
- Toys, exercise wheels, bedding, and boxes changed weekly
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

Behavioral testing

- Weaning
- Divide into EE/con cages
- 2 months
- 8.5 months

Sacrifice/dissection
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

Graph showing distance in cm over consecutive days of training for Control and Enriched conditions, with different genotypes indicated by colors and markers.
Standard Morris Water Maze

**Average Distance**

**Time in Quadrant, %**

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**Legend:**
- NTg
- PS1dE9
- APPswe
- APPswe/PS1dE9

* Indicates significant difference.
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

![Graph showing distance over consecutive training trials for Control and Enriched groups with different markers for NTg, PS1dE9, APPswe, and APPswe/PS1dE9.]

**Average Distance**

- **Control**
  - NTg: [Graph data]
  - PS1dE9: [Graph data]
  - APPswe: [Graph data]
  - APPswe/PS1dE9: [Graph data]

- **Enriched**
  - NTg: [Graph data]
  - PS1dE9: [Graph data]
  - APPswe: [Graph data]
  - APPswe/PS1dE9: [Graph data]
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

- **Control**
- **Enriched**

Errors in Trials 2-5:
- Control
- Enriched

Legend:
- NTg
- PS1dE9
- APPswe
- APPswe/PS1dE9

Bar plots showing the number of errors over consecutive training trials for control and enriched conditions.
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. Wefes3 and H. Potter1,3

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. Sisodia1,*
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
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
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