

# Aspects of Neurogenesis: Lessons from Childhood Cancer and Adult Impact Injury

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and

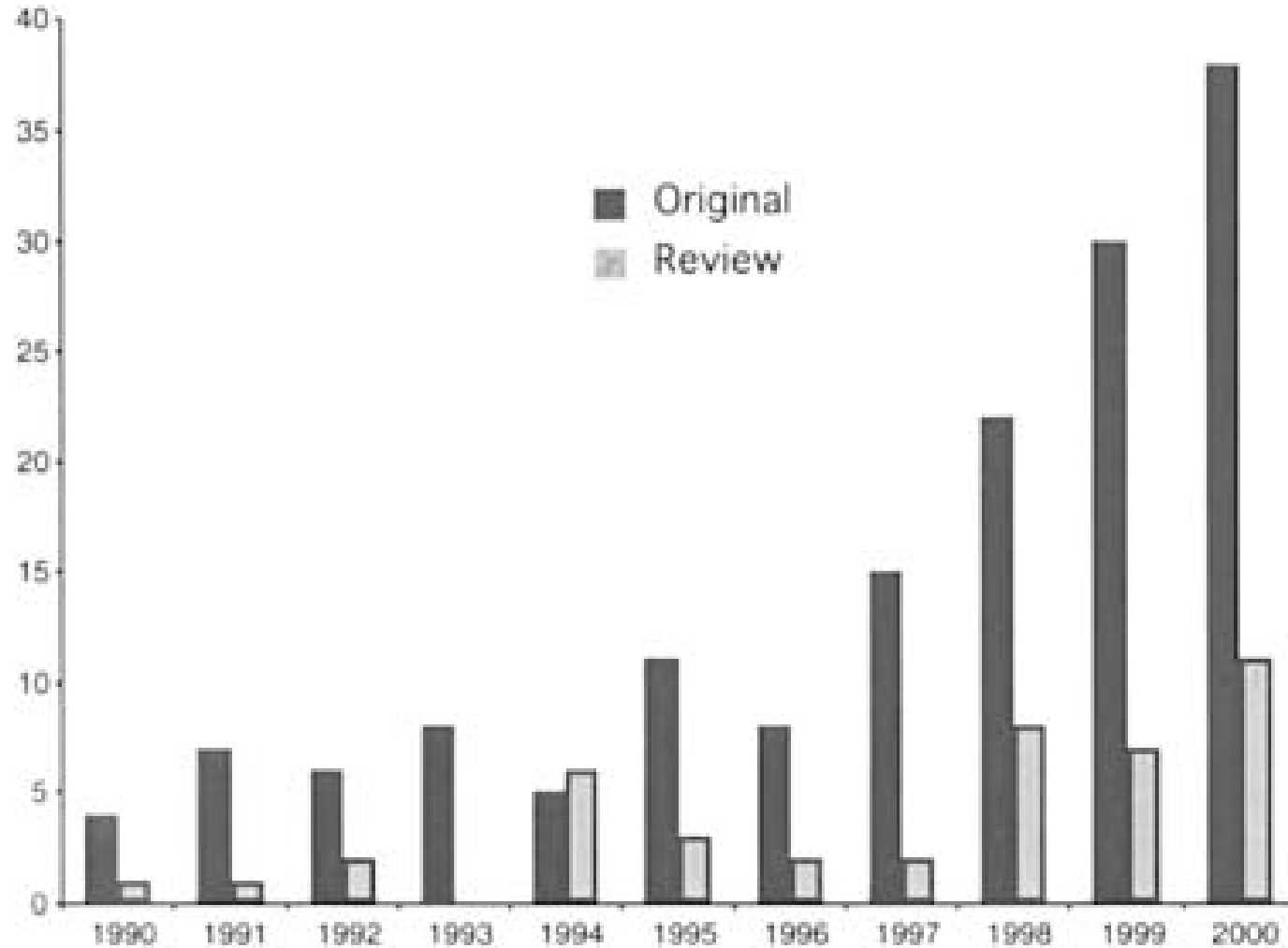
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# Overview

- Adult neurogenesis: What, Where, and Why
- Factors that modulate neurogenesis
- Potential role of neurogenesis in recovery from brain injury (XRT for brain tumors and traumatic brain injury)

# Rapid Rise in Neurogenesis Research



# Adult Neurogenesis

What?

Where?

Why?

“You are born with all of the neurons you are ever going to have.”



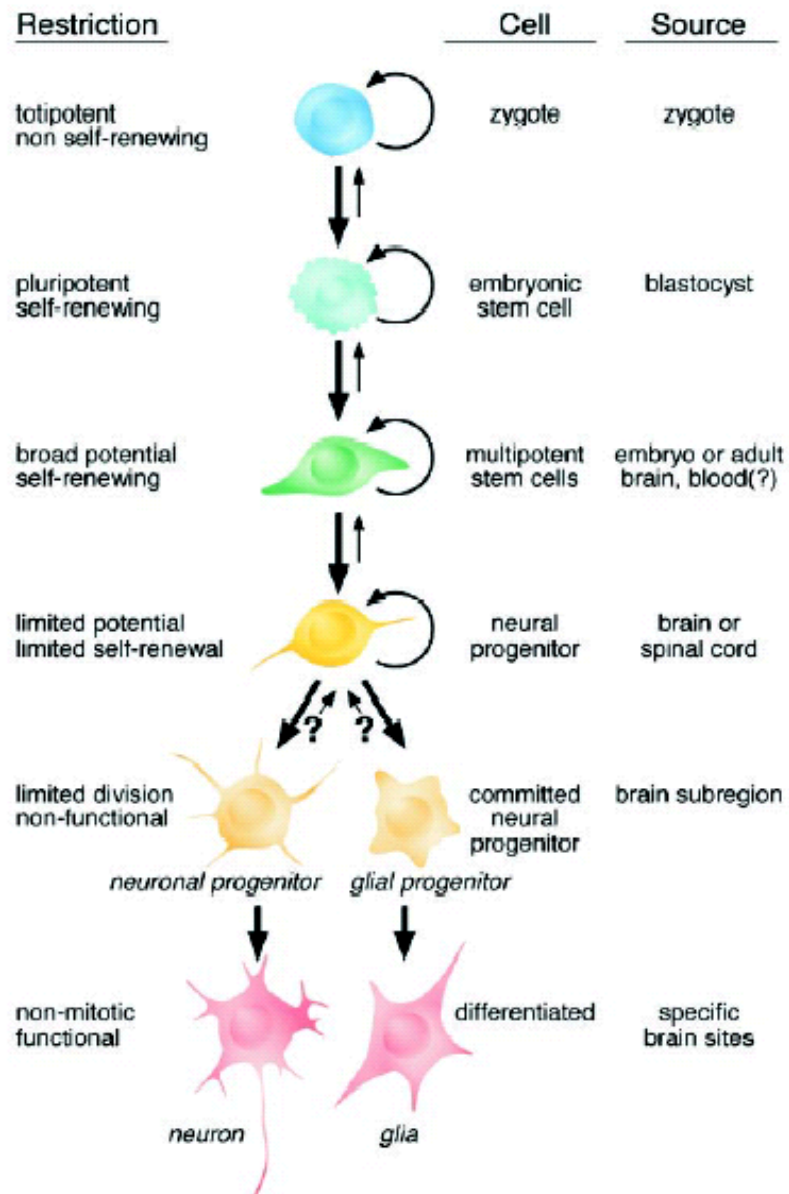
- Evidence that this might not be true was reported as early as 1901 (Hamilton)
- More evidence in the 1960s (Altman)
- Convincing evidence in 1990s (Gould, Gage, and others)

“Throughout adulthood, proliferative neural stem cells remain widespread in the CNS”.

What is a neural stem cell?

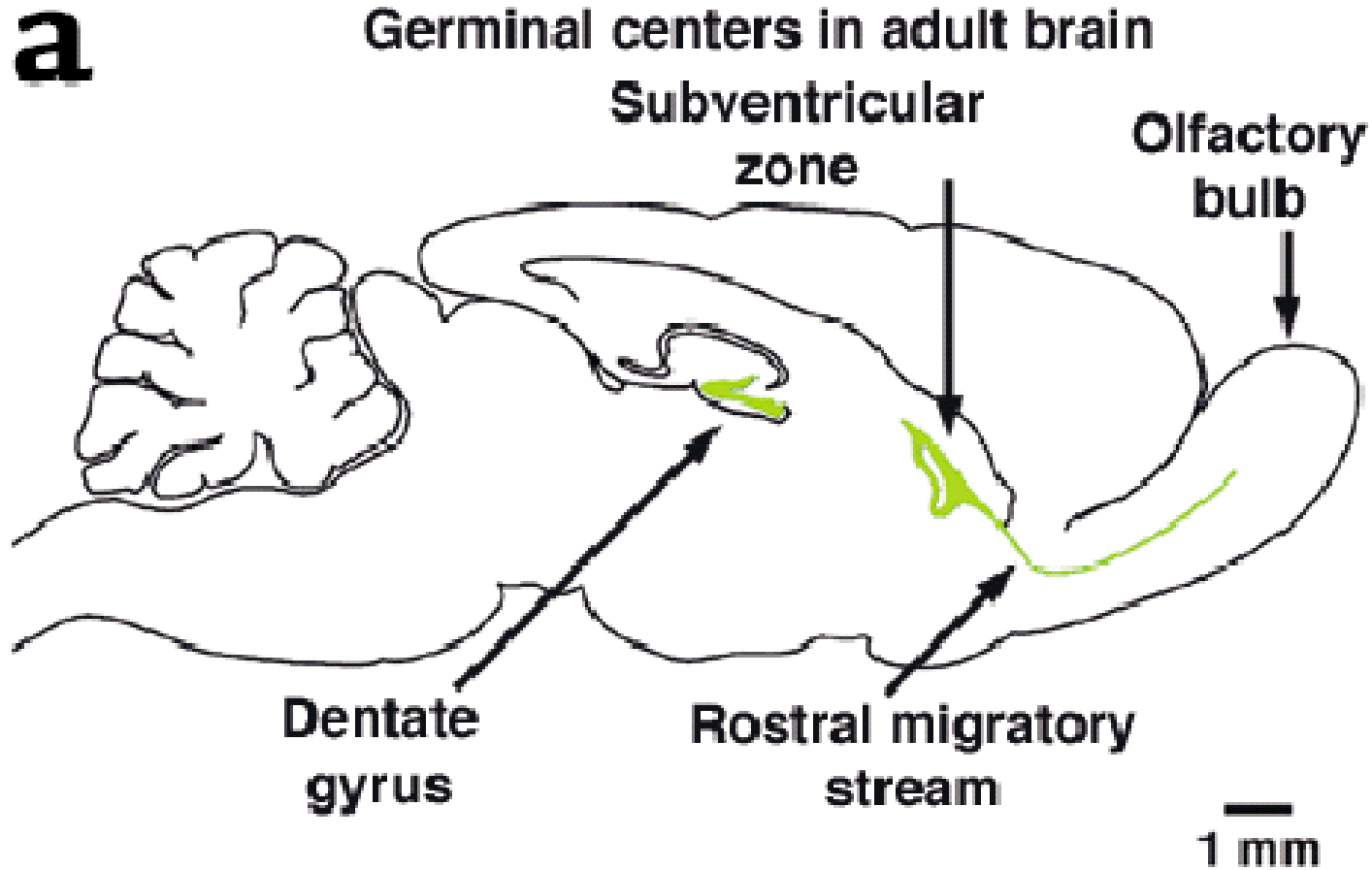
1. It has some capacity for self-renewal
2. It can give rise to neural cells other than itself through asymmetric cell division (multilineage potential)

## Potential Stem Cells with Neural Capability



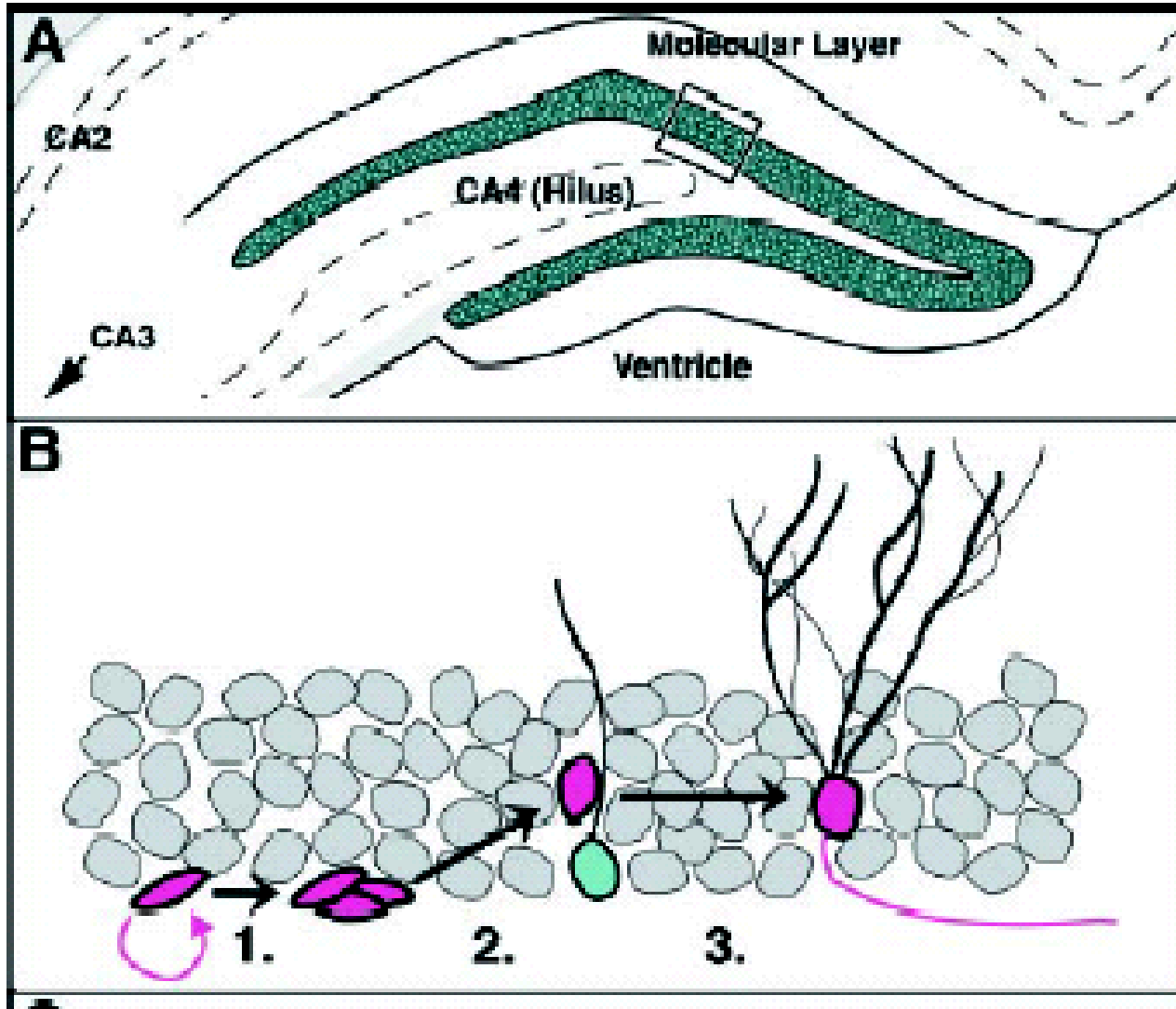
Gage, FH. 2000.  
Mammalian Neural Stem  
Cells. Science: 287:  
1433-1438.

# Neurogenesis in Adult Brains



Hallbergson et al., 2003

# Origin and Migration of Stem Cells in the Hippocampus. Gage, FH. 2000.



45% migrate into the granule cell layer

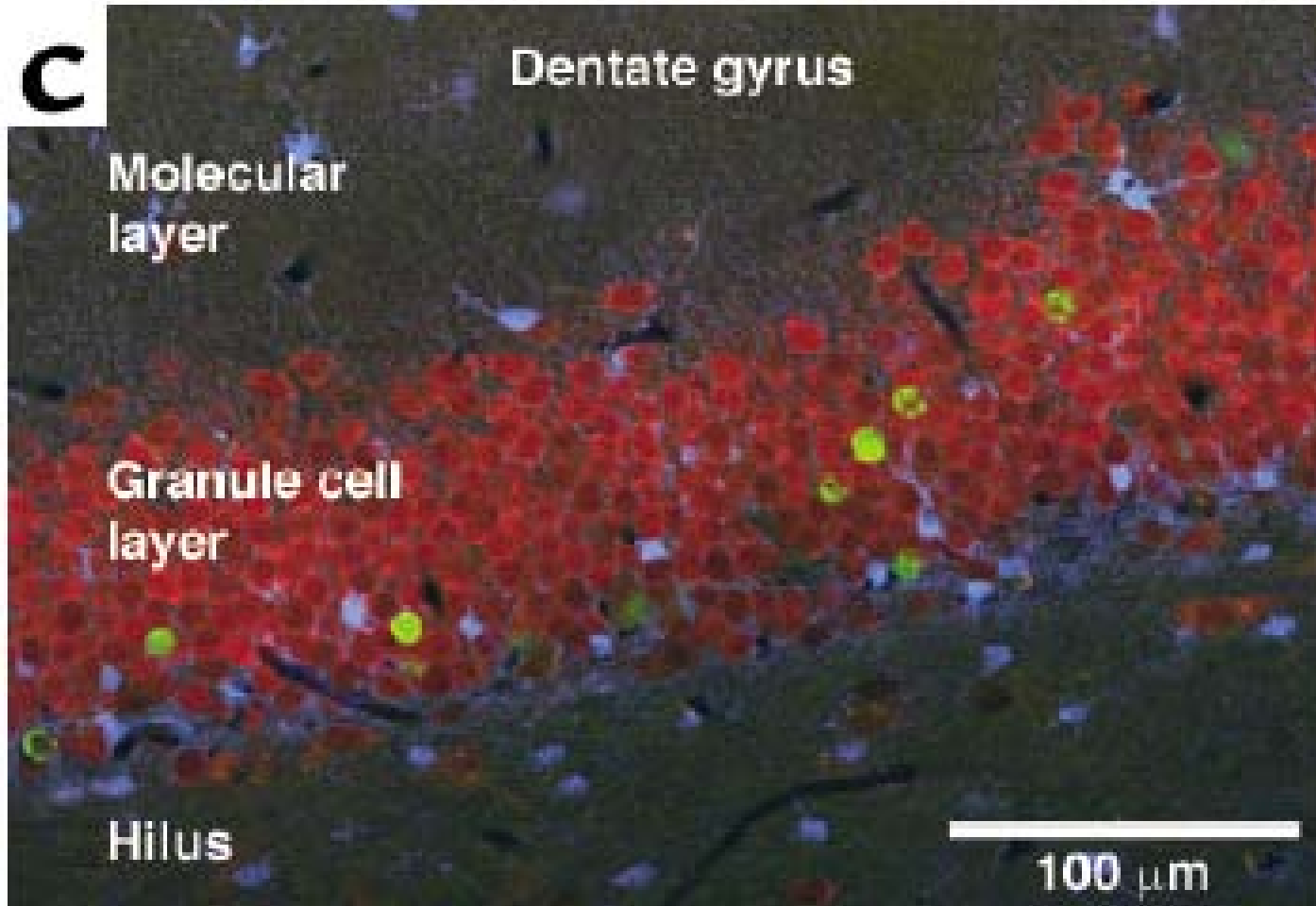
25% migrate into the hilus

30% remain in the subgranular zone

# Proliferation and Survival of Neural Stem Cells in the Dentate

- 9,000 new cells per day = 270,000/month
- 20% of the total in the granule cell layer
- But..... 50% die within the first 2 weeks
- Some new cells survive for months

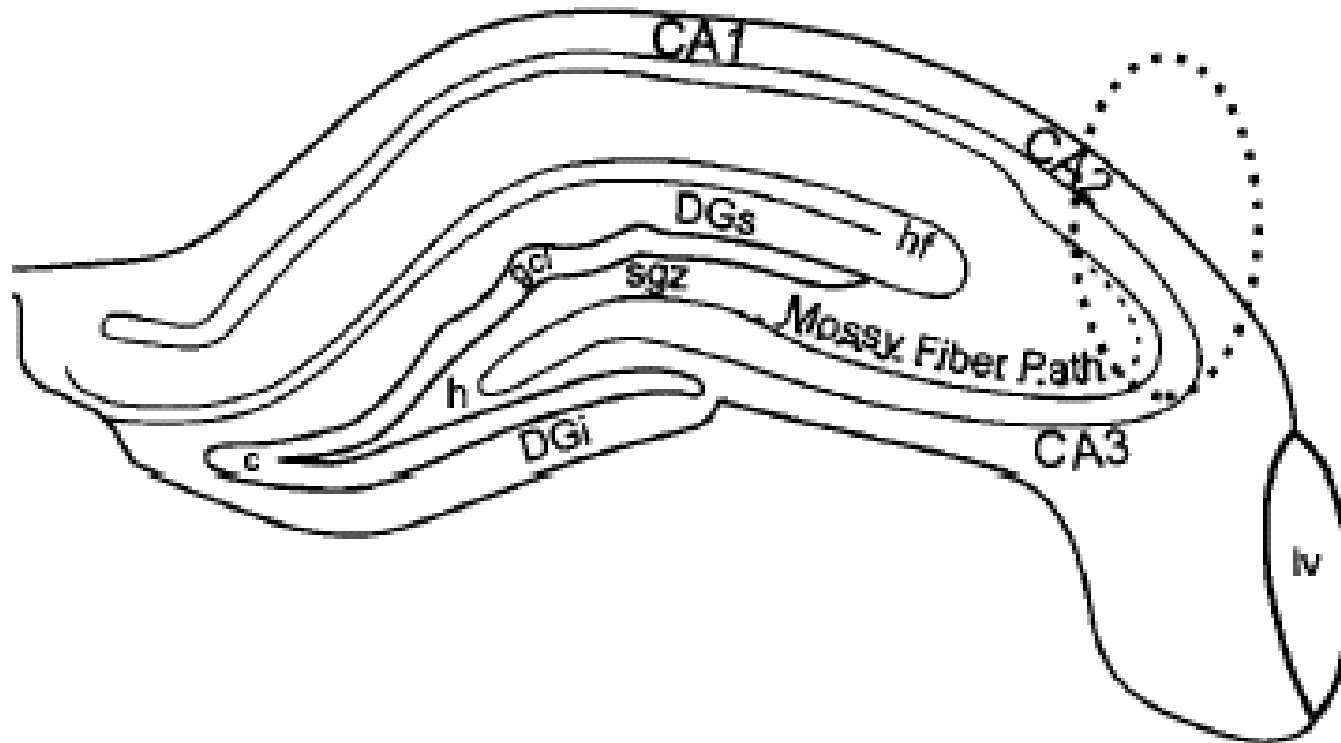
# Fate of Neural Stem Cells in the Dentate Gyrus



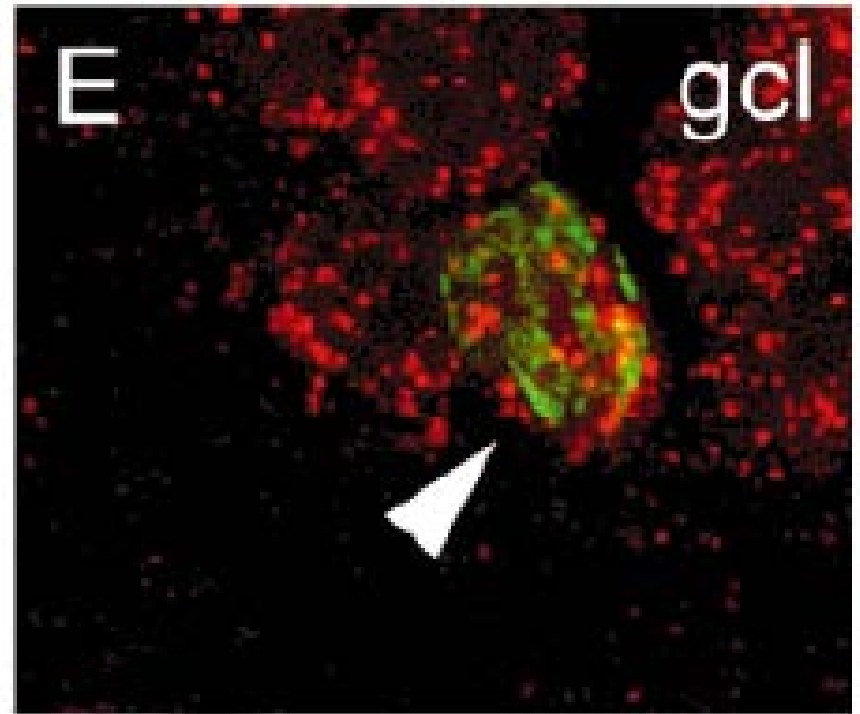
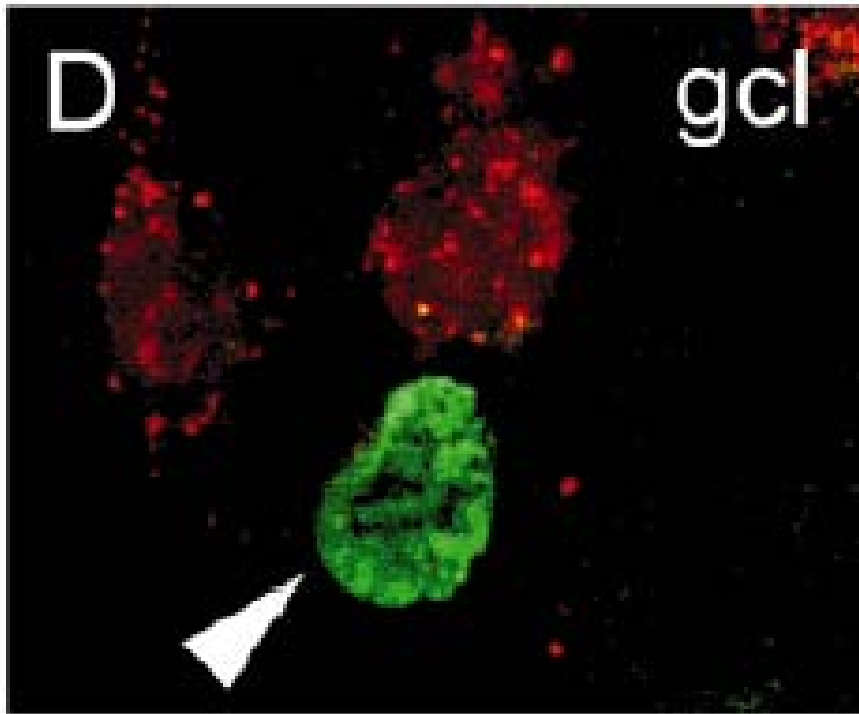
55% neurons  
10% astrocytes  
35% immature

Hallbergson et al., 2003

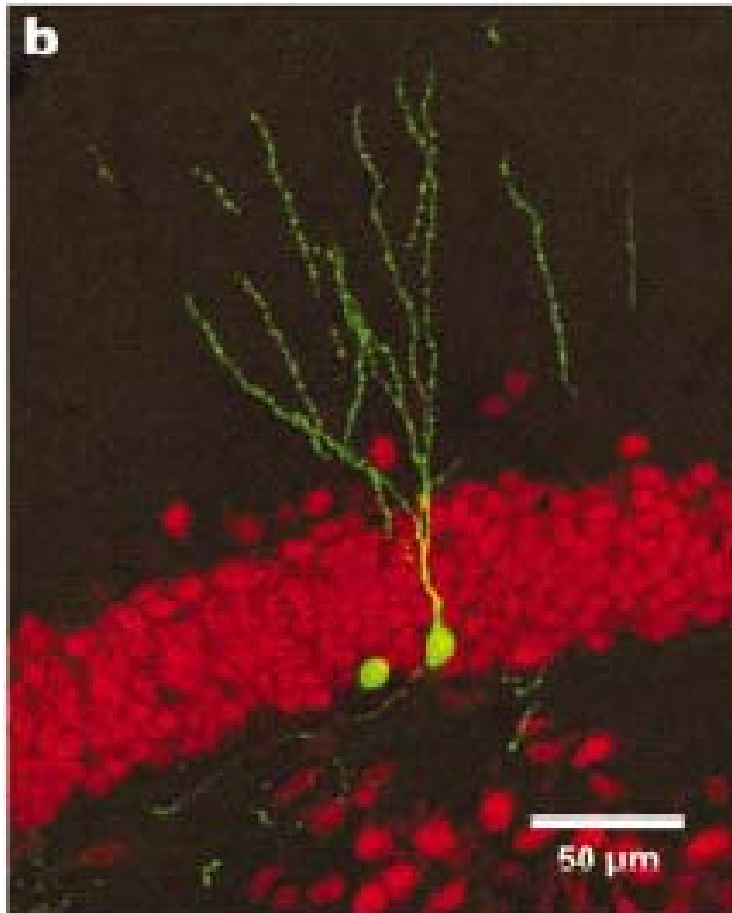
**Do the newly born neurons make appropriate connections?** Hastings and Gould, 1999



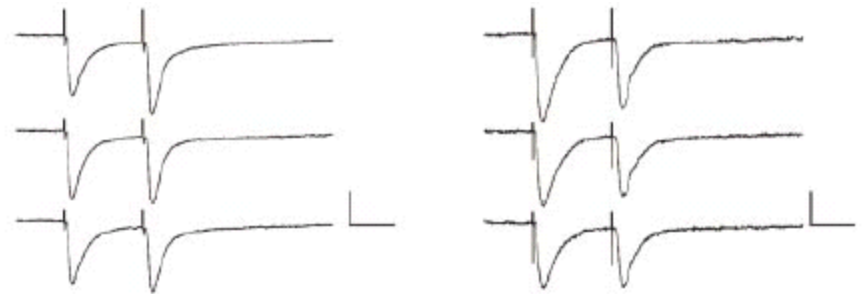
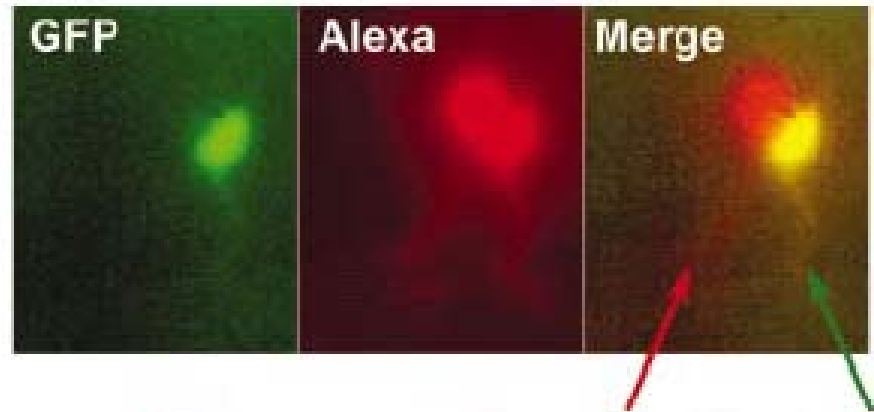
Yes. Beginning around 10 days after birth,  
peaking around 17 days.



# Do the neural progenitors make functional connections? Van Praag et al., 2002



## Live hippocampal slice



# What do the adult-generated neurons in the hippocampus do?

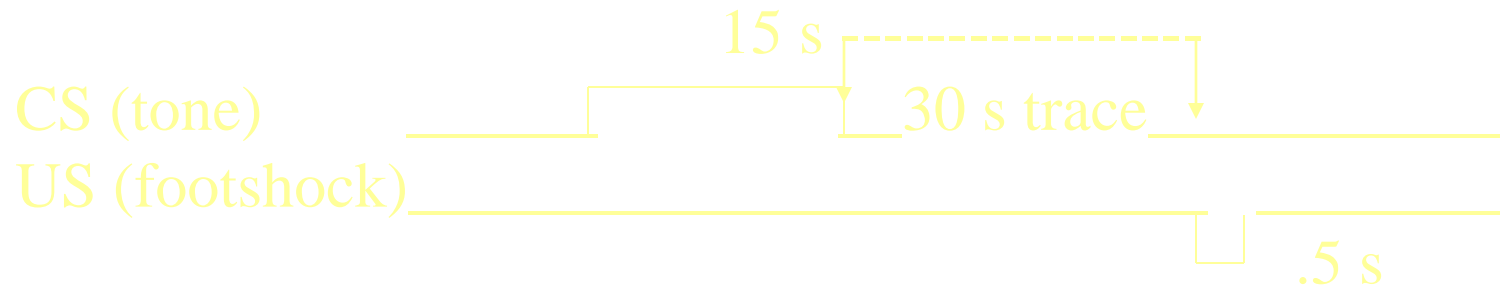
- *Hypothesis 1*: a vestige of evolution.
- *Hypothesis 2*: limited capacity for self-renewal is important for hippocampal-dependent learning and memory

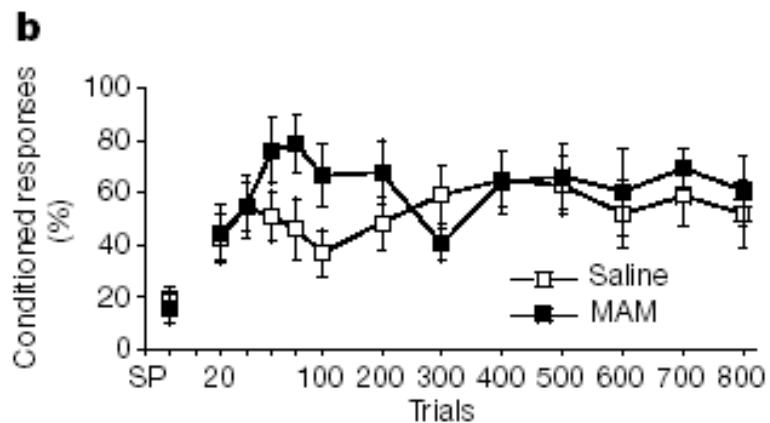
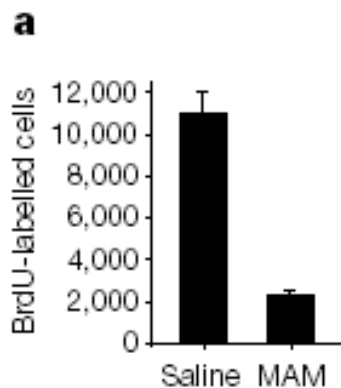
# **Neurogenesis may relate to some but not all types of hippocampal-dependent learning.**

Shors et al., 2002

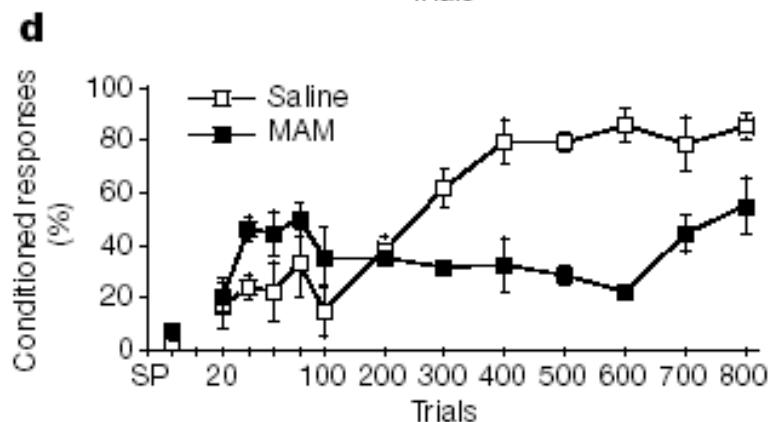
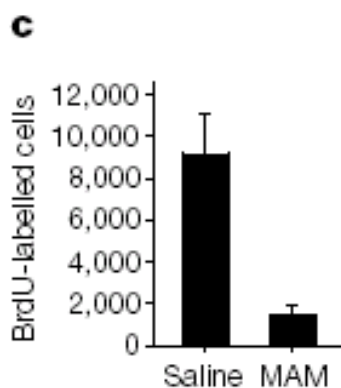
- Reduction did not effect
  - Spatial navigation learning in a Morris Water Maze
  - Contextual fear conditioning
- But reducing neural progenitors did impair trace fear conditioning

# Trace Fear Conditioning

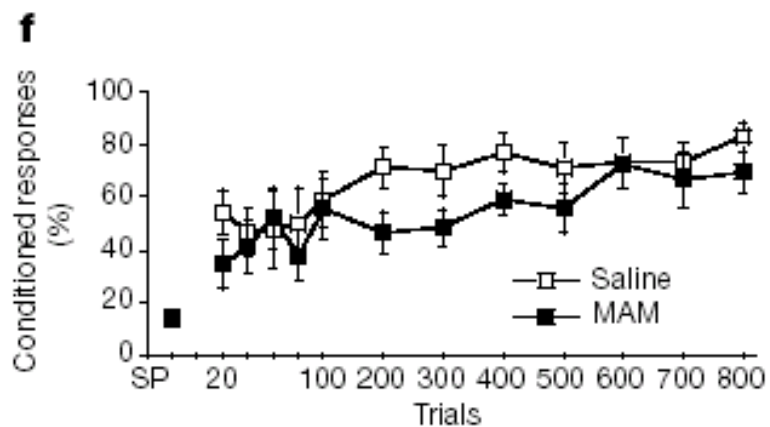
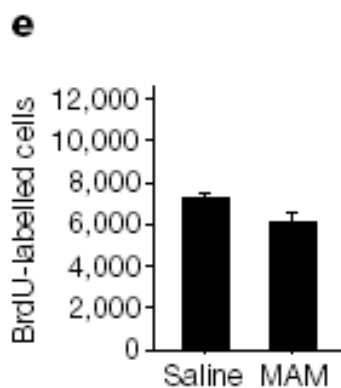




6 days



14 days



21 days

# Summary

- Neural stem cells in the hippocampus are able to generate adult neurons with properties similar to mature neurons.
- They appear to be important for specific types of learning and memory.

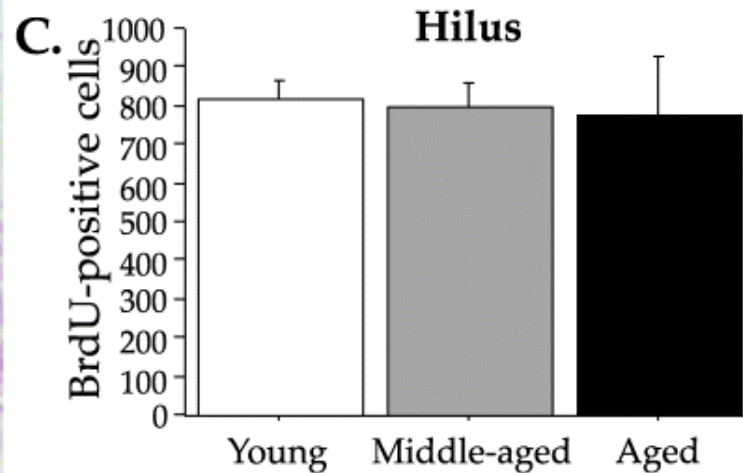
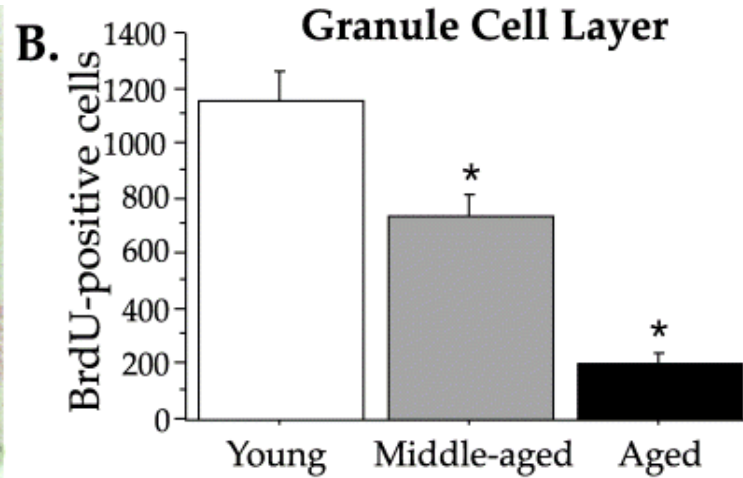
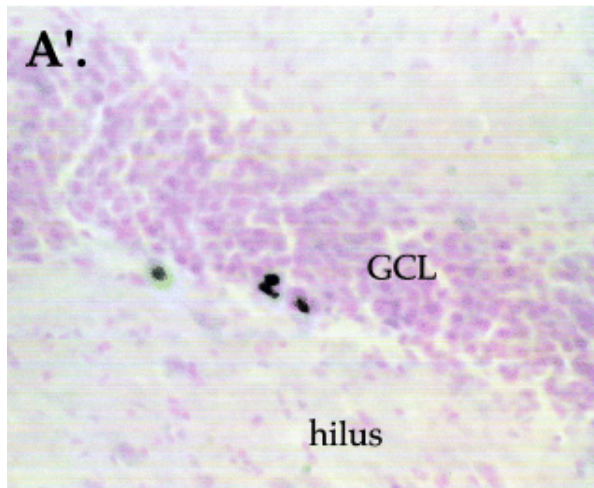
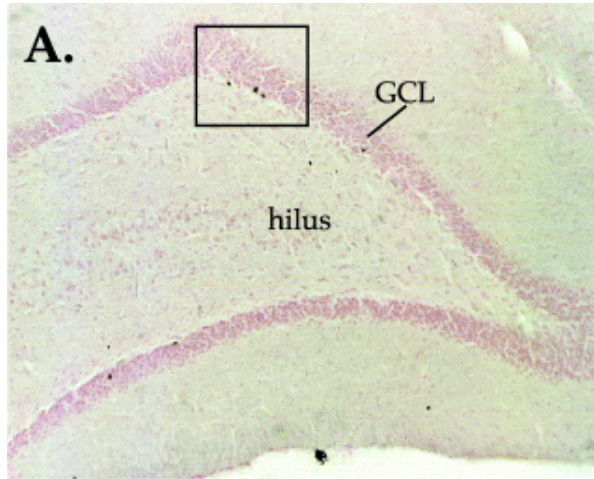
# Down- and Up-Regulation of Neurogenesis

- Several factors, experimental variables have been shown to decrease and/or increase the rate of neurogenesis, or the retention of newly created neural cells
- Most research has looked only within the hippocampus – primarily dentate gyrus
- Difficult to determine whether these factors are necessary, sufficient for NG, or simply correlate w/ NG

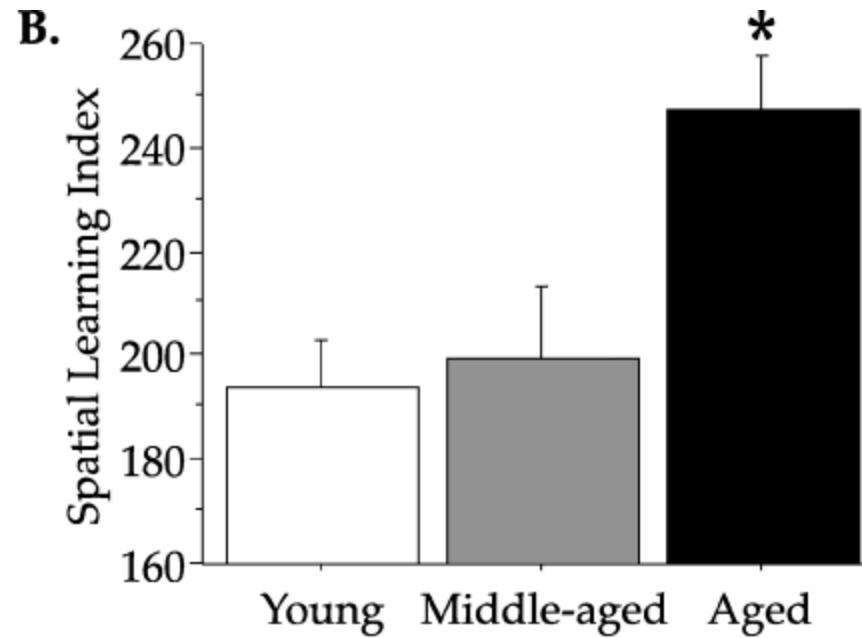
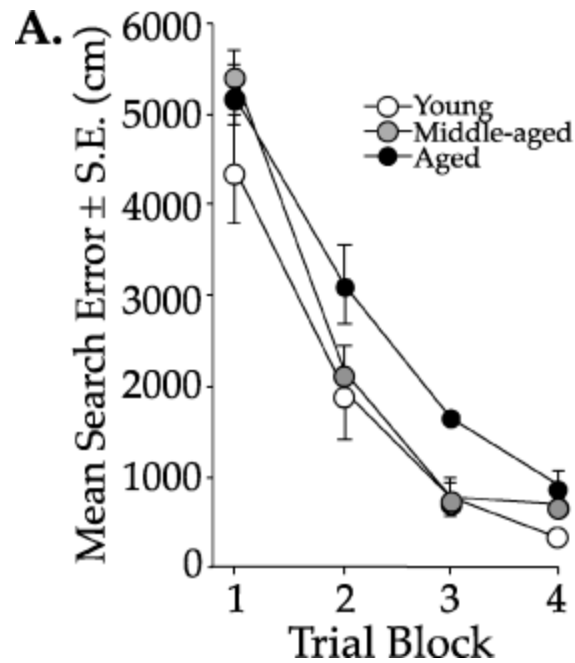
# Down-Regulation of Neurogenesis

- Age
- Stress
- Specific substances

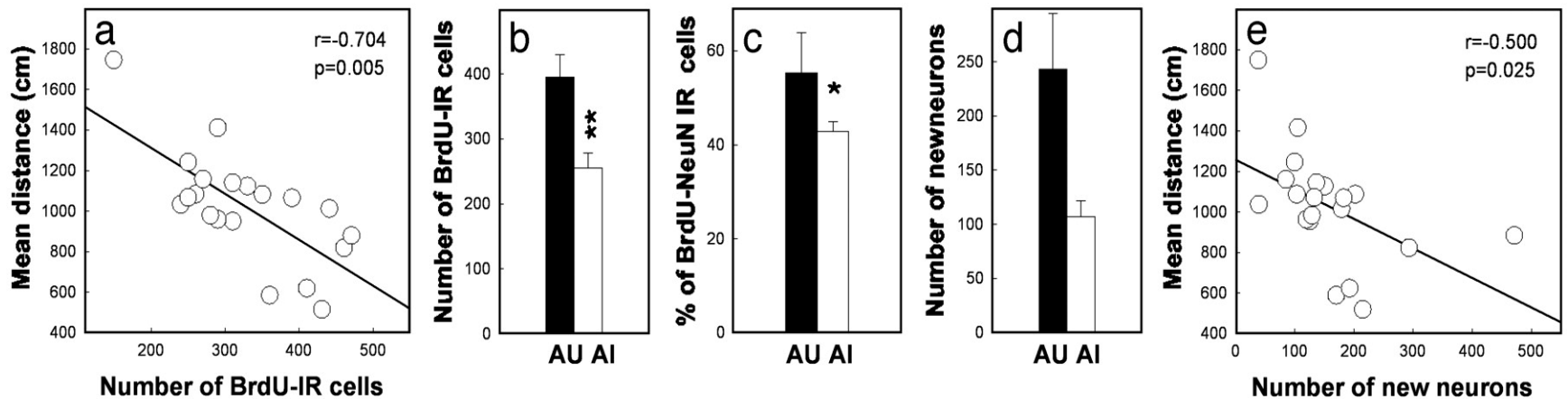
# Aging and NG



# Aging, NG and Water maze performance



# Neurogenesis and Learning in Aged Rats

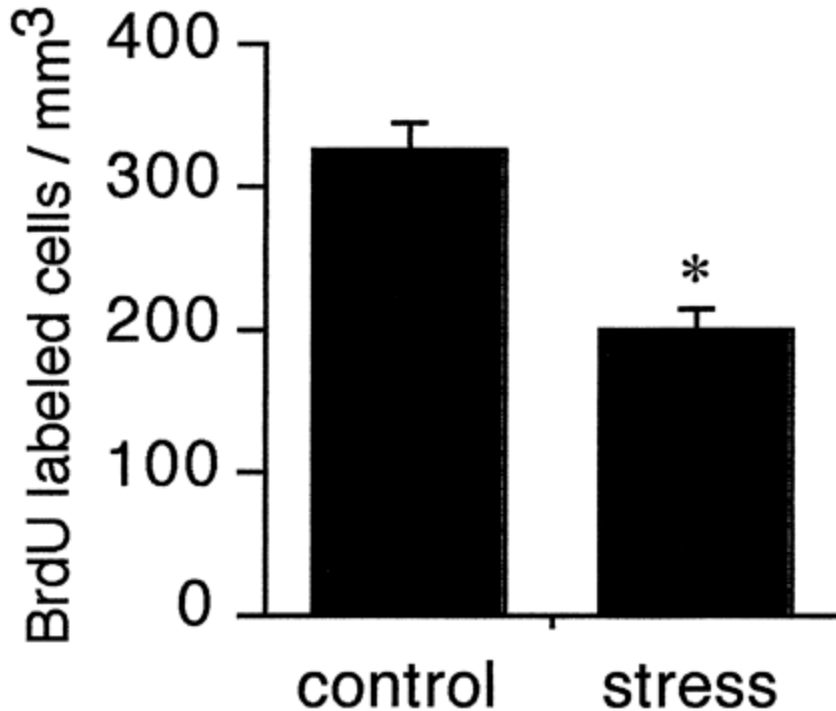


Survival and differentiation of newly generated cells in the granule cell layer. Performance on MWM as a function of new cells/neurons. Differences between upper 30% ("Age Unimpaired" - AU) and lower 30% ("Age Impaired" - AI) animals on cell counts.

# Down-regulation of Neurogenesis: Stress

- Experimental restraint – Small decrease in NG
- Natural predator (e.g. odor)- Decrease in NG
- “Psychosocial” animal stress - Decrease in NG

# Predator Stress and NG



A single exposure to a resident-intruder model of stress results in a significant decrease in the number of BrdU-labeled cells in the dentate gyrus of the intruder marmoset monkey.

# Adrenal Steroids Mediate Stress Effect on NG

- Adrenal steroid production lowest in early prenatal period – NG highest; vice versa in older animals
- Experimental increases in adrenal steroid produce reductions in NG
- Removal of adrenal steroids (adrenalectomy) associated w/ increase in NG

# Down-regulation of Neurogenesis: Substances

- Methylazoxymethanol (MAM)
  - Causes newly proliferated neurons to die
  - Decreases # of newly generated cells in the dentate gyrus
  - Decreases hippocampal learning

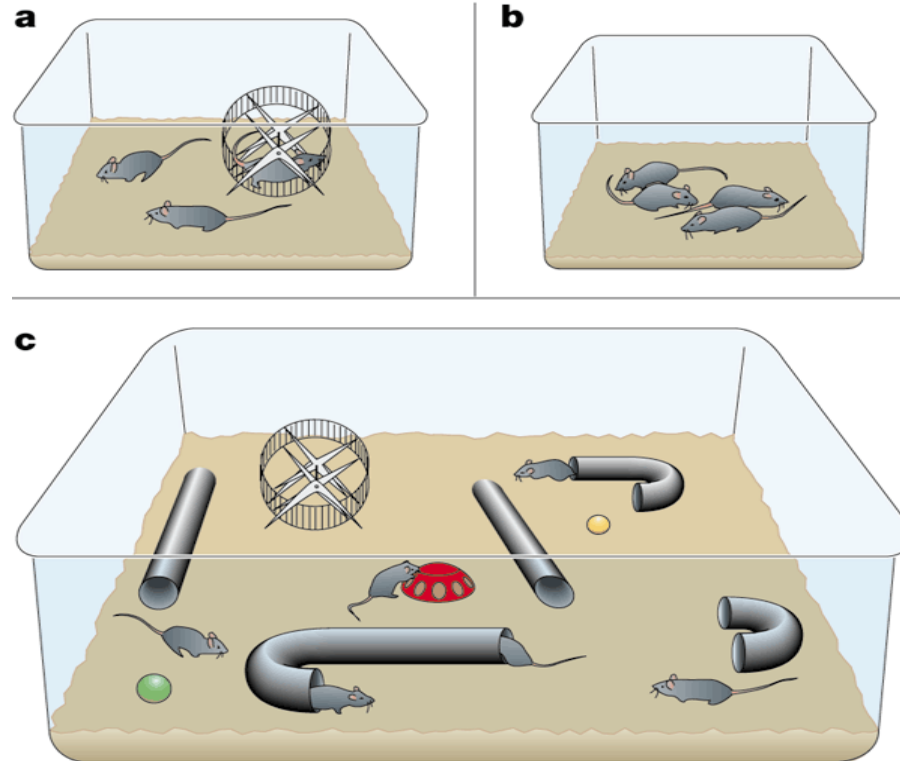
# Up-Regulation of Neurogenesis

- Environmental enrichment
  - Physical activity
  - Stimulation & learning
- Serotonin, SSRI's
- Estrogen
- Dietary restriction

# Environmental Enrichment

- Typical animal model involves multiple stimulating opportunities - activity and exploration (learning)
- Compared to laboratory environment of housing without typical activity or stimulation
- No single variable (social interaction, general activity, observation) accounts for effects on NG

# Environmental Enrichment



Nature Reviews | **Neuroscience**

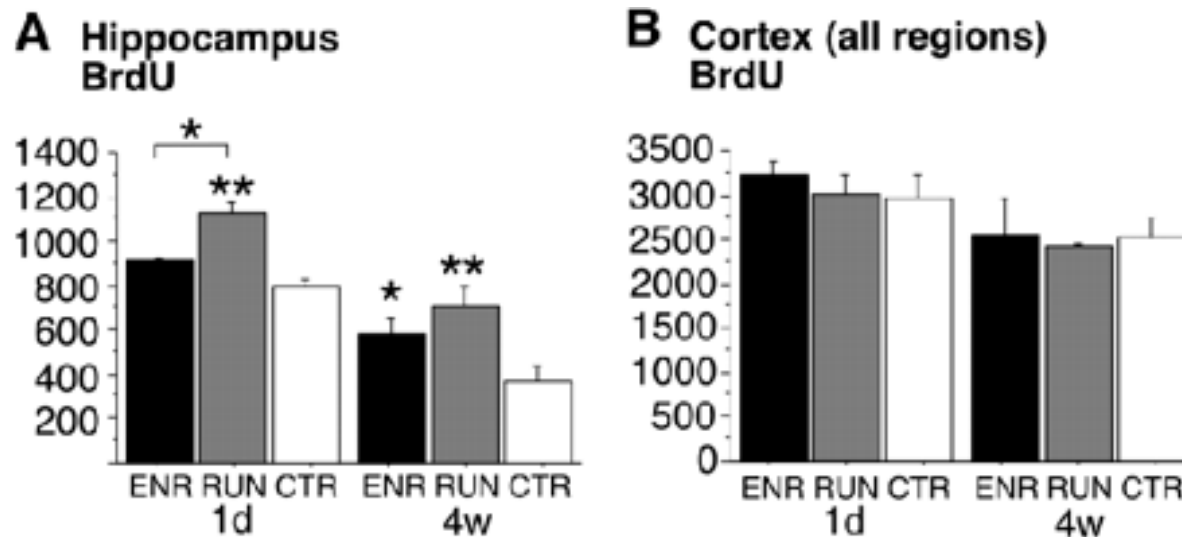
Van Praag, Kempermann & Gage, *Nature*, 2000

# Environmental Enrichment – Key Components

- Learning
  - Acquisition of hippocampus-dependent learning
- Physical activity
  - May be confounded by stress

# Environmental Enrichment

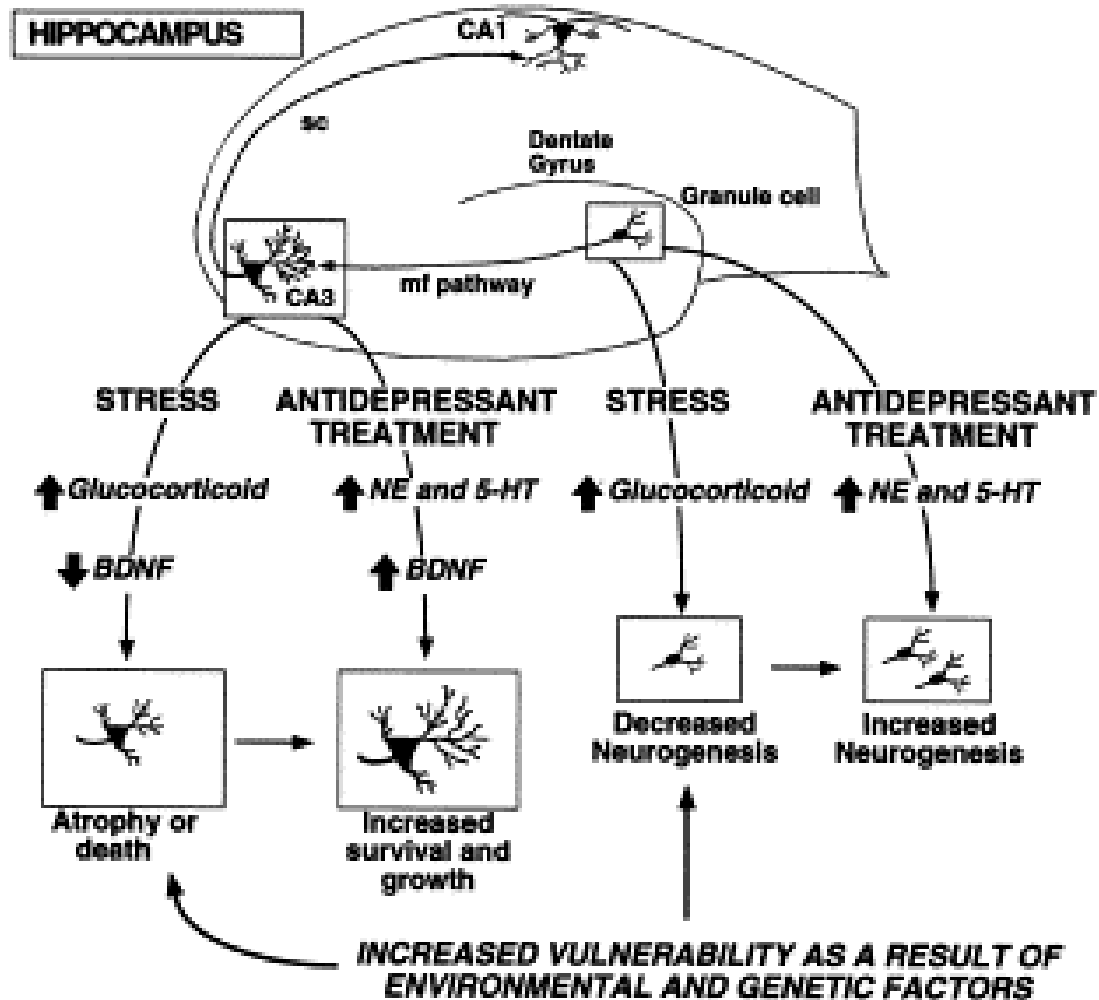
- Activity vs. enriched environment



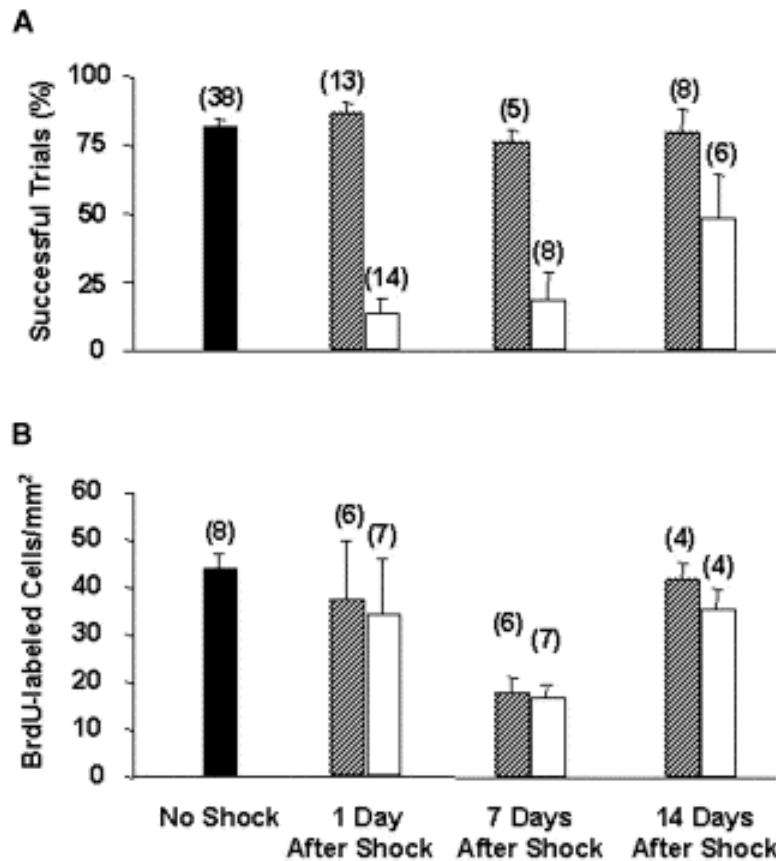
# Effects of Learning (Hippocampal-dependent) on NG

- $\geq 4$  days learning  $\longrightarrow$  2x increase in new neurons
- Effective only during time of maximal apoptosis
- Assoc. w/ decrease in rate of apoptosis
- No increase in NG after learning is complete

# Stress, Depression and Neural Plasticity (incl. NG)



# ...but some contradictory evidence about depression and neurogenesis



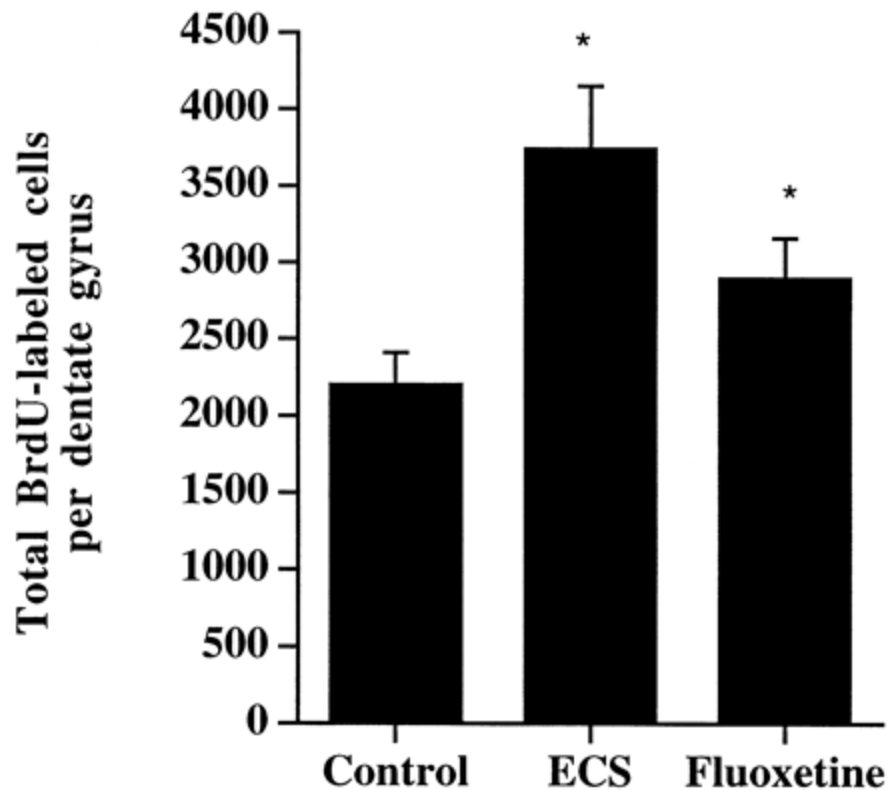
Development of learned helplessness (as an animal model of depression) showed no effect on dentate gyrus neurogenesis.

Black = control

Gray = non-learned helpless

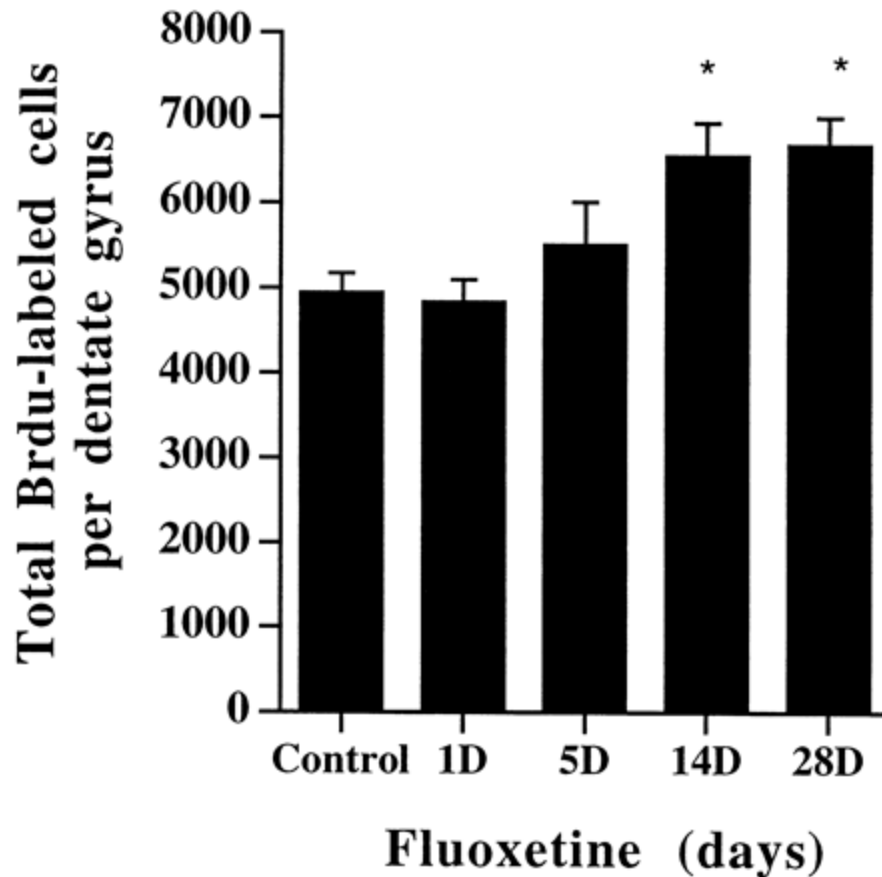
White = learned helpless

# Effects of SSRI's on NG



The number of BrdU-positive cells is increased 4 weeks after chronic antidepressant treatment.

# Effects of SSRI's on NG



Chronic, but not acute, fluoxetine administration increases BrdU labeling in the adult hippocampus.

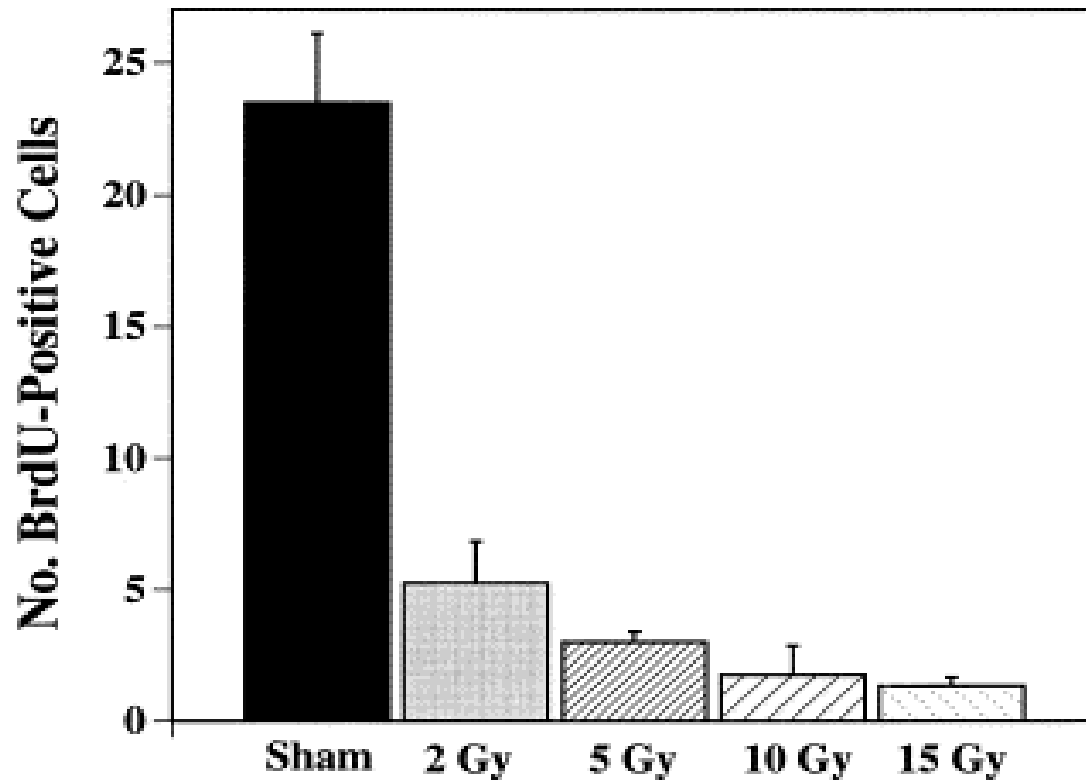
# Potential Role Of Neurogenesis In Recovery From Brain Injury

- Cranial Irradiation for Brain Tumors
- Traumatic Brain Injury

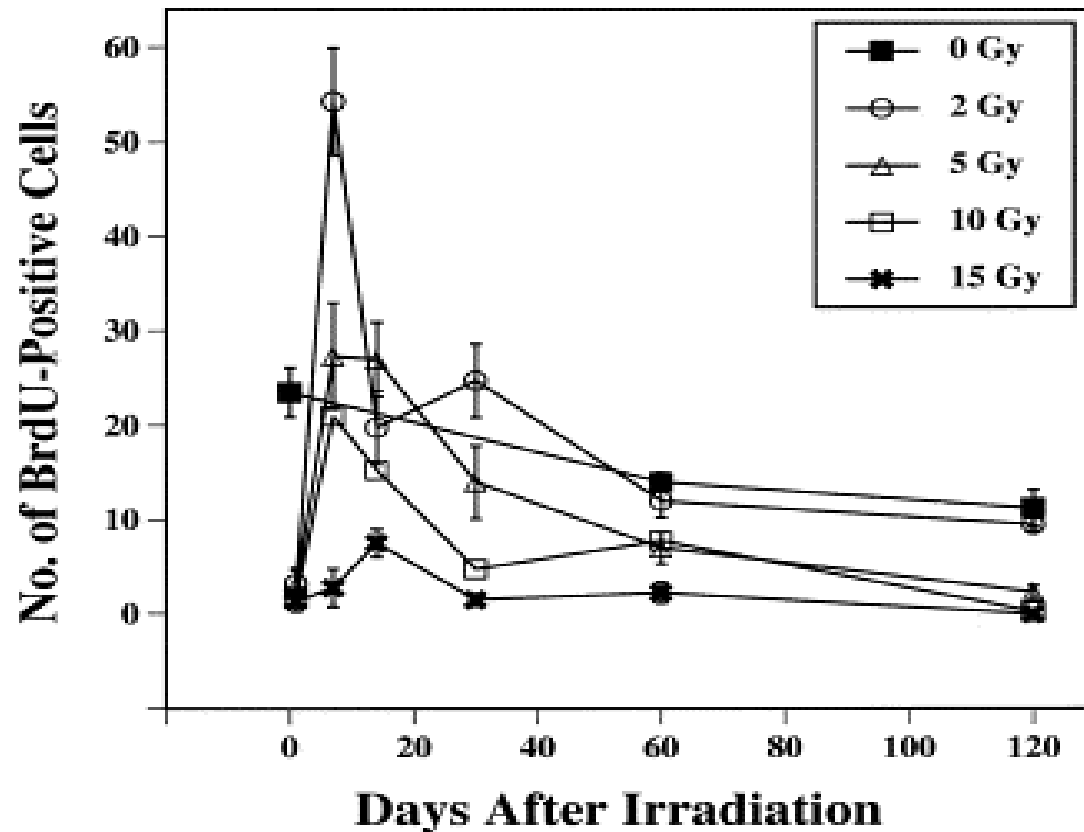
# Cranial Irradiation and Neurogenesis

- High dose leads to ablation
- Lower doses lead to inflammation
- Lower doses leads to apoptosis of “sensitive” cells

# Cranial Irradiation and Neurogenesis



# Cranial Irradiation and Neurogenesis



# Performance on virtual Morris Water Task

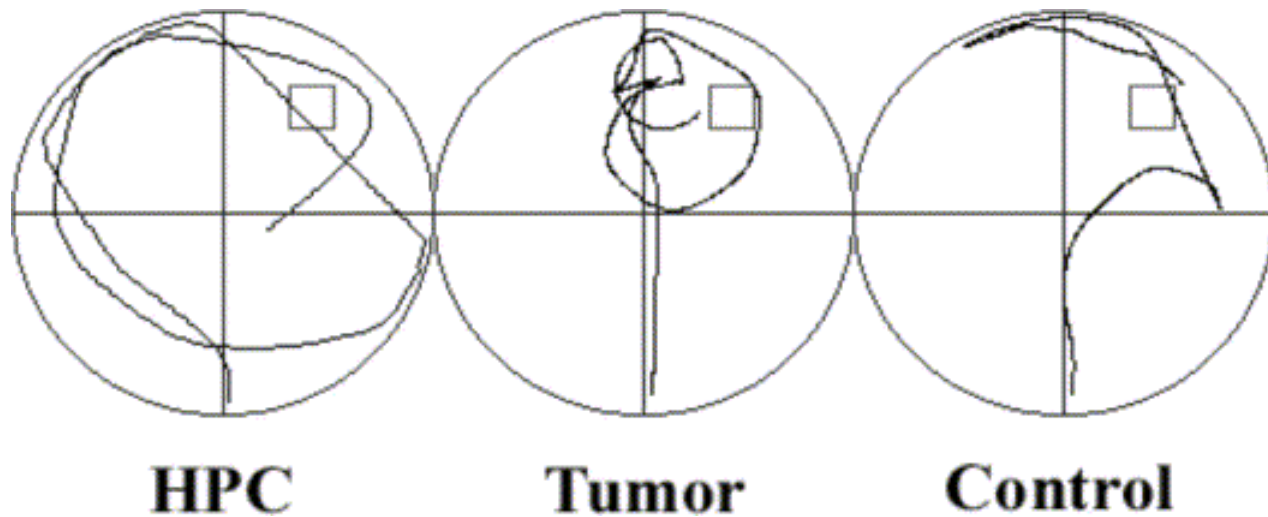
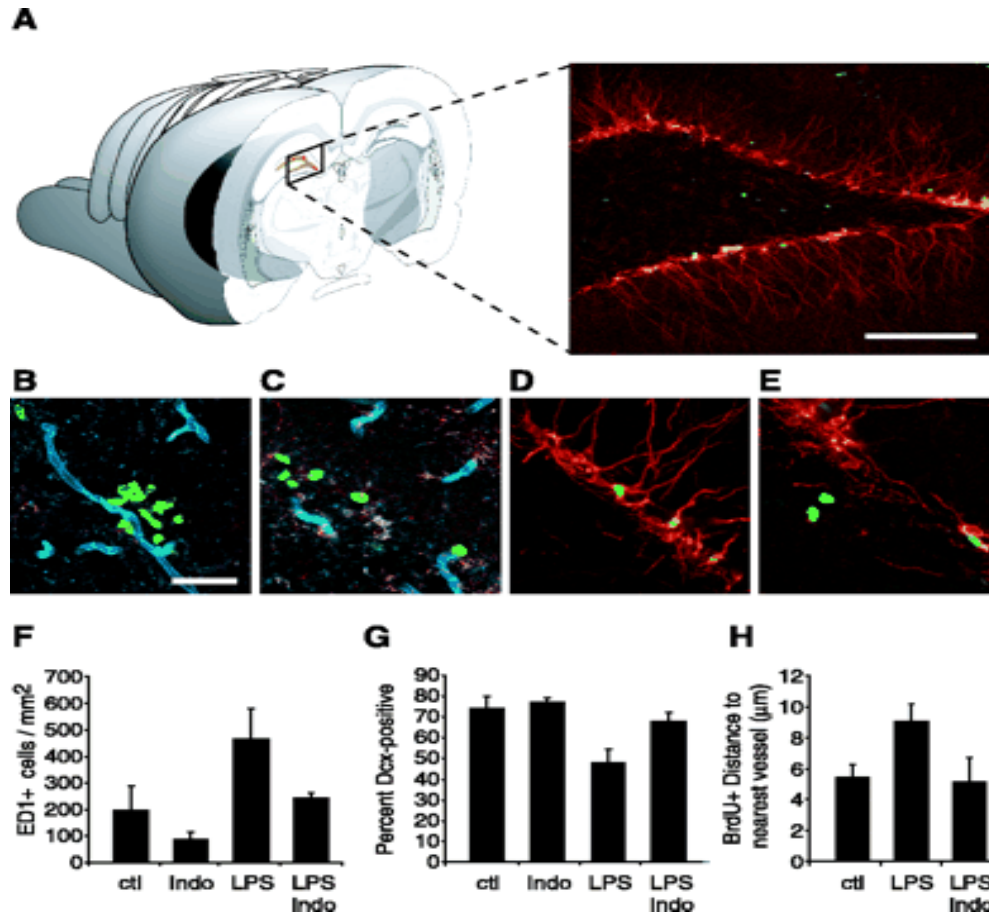
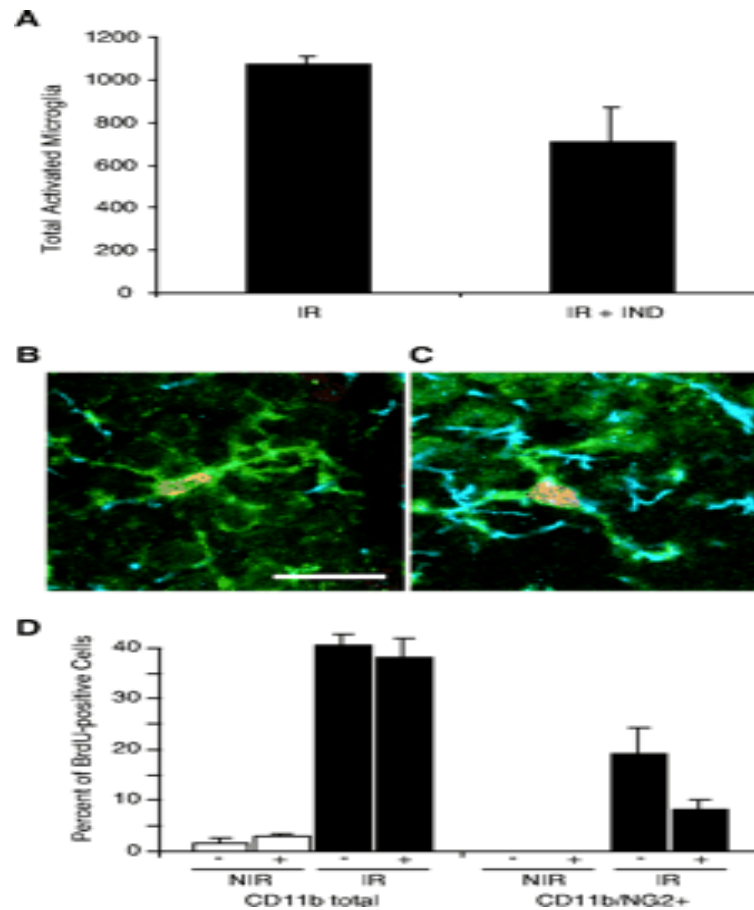


Fig. 3. Probe trial swim paths from the first probe trial of the median individual in each group, as determined by probe trial performance. Note the lack of a preference for the correct quadrant by the individual from the HPC (hippocampal damage) group.

# Inflammation (microglial activation) and NG

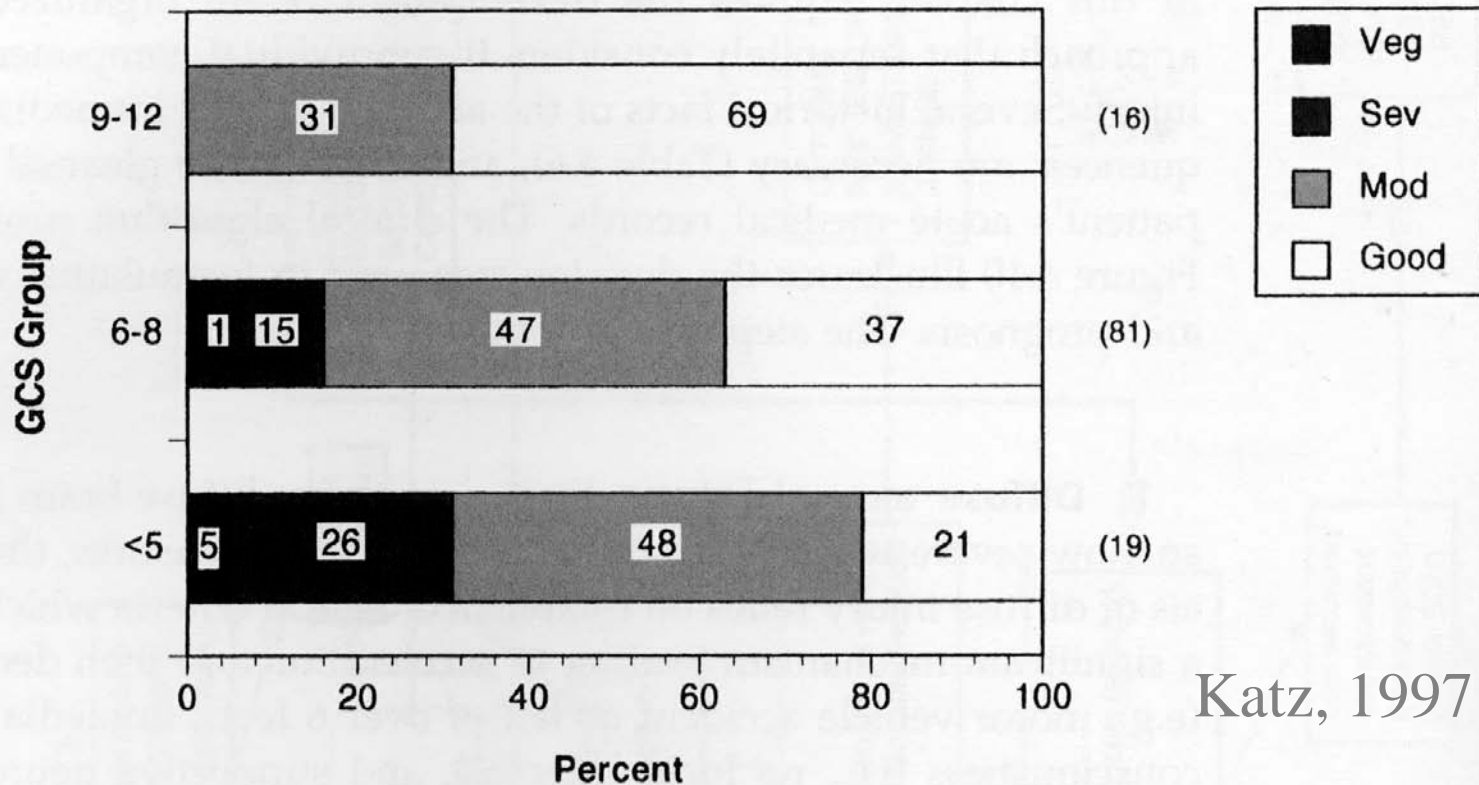


# Blockade of microglial activation: Effect on NG



# Recovery is Often Incomplete following TBI

**12 Month Outcome by GCS Class**  
(Patients with moderate to severe DAI, n=116)

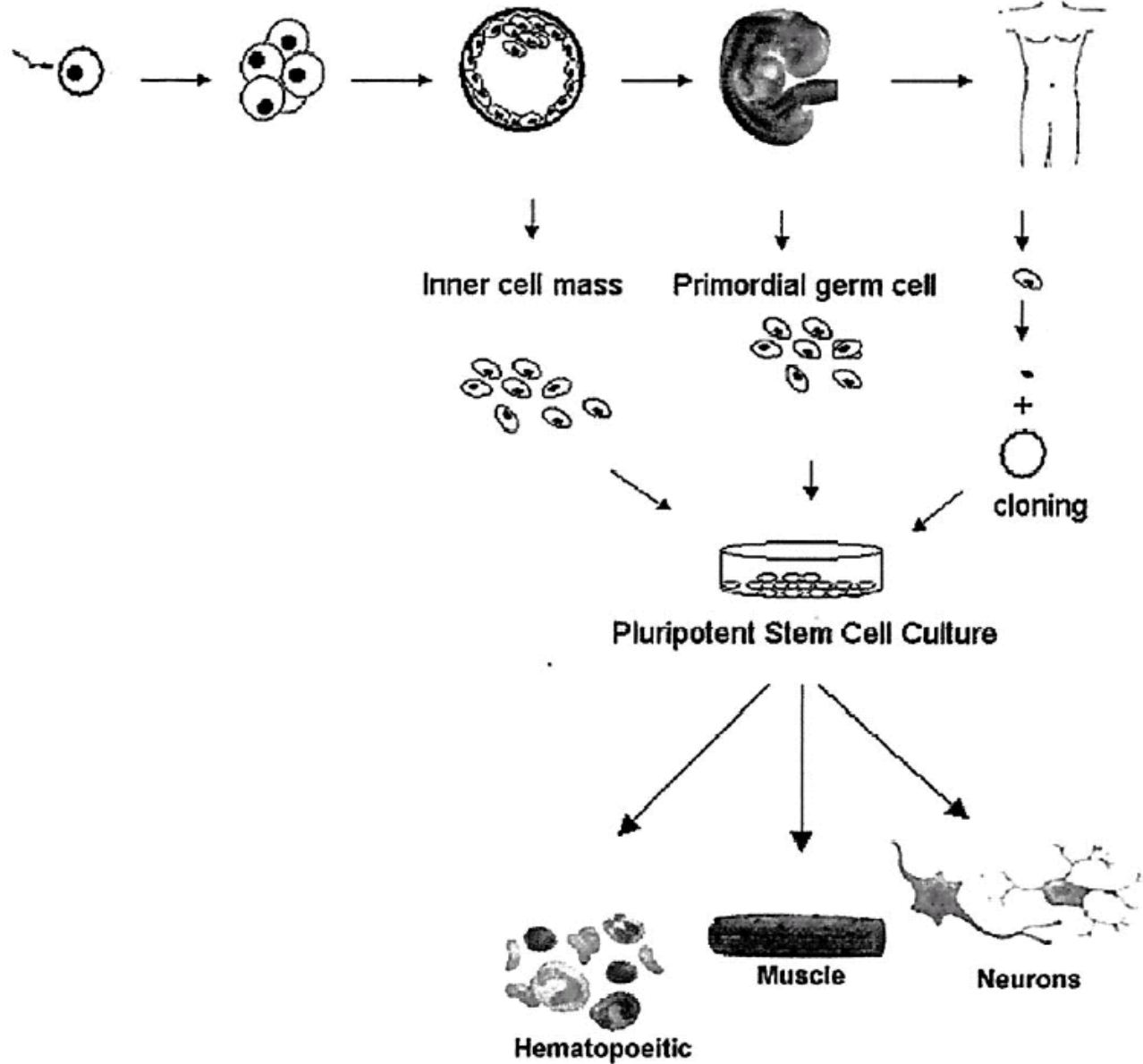


Katz, 1997

# Neuronal Replacement Therapy

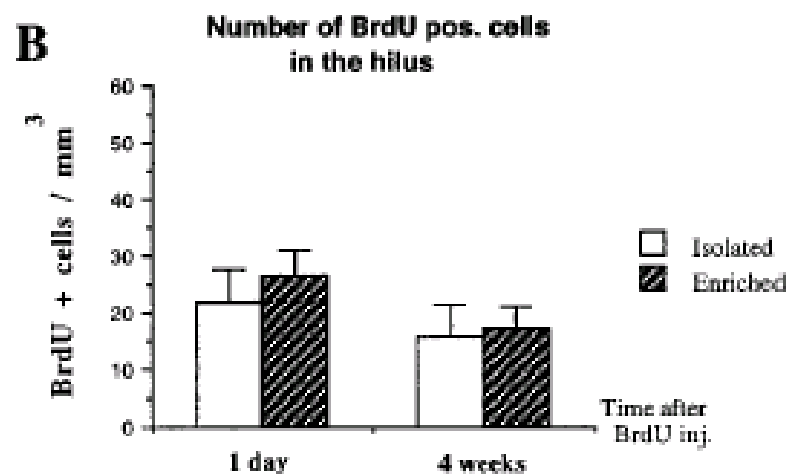
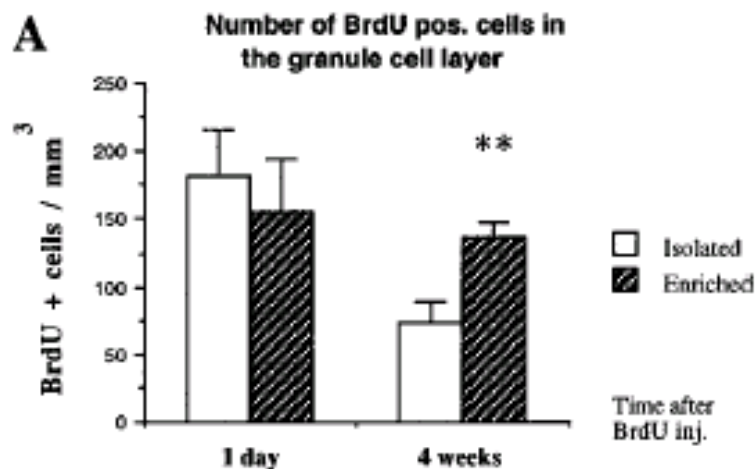
- Embryonic stem cells
- Somatic (adult) stem cells
- Endogenous neural stem cells

# Exogenous stem cells as a source of replacements

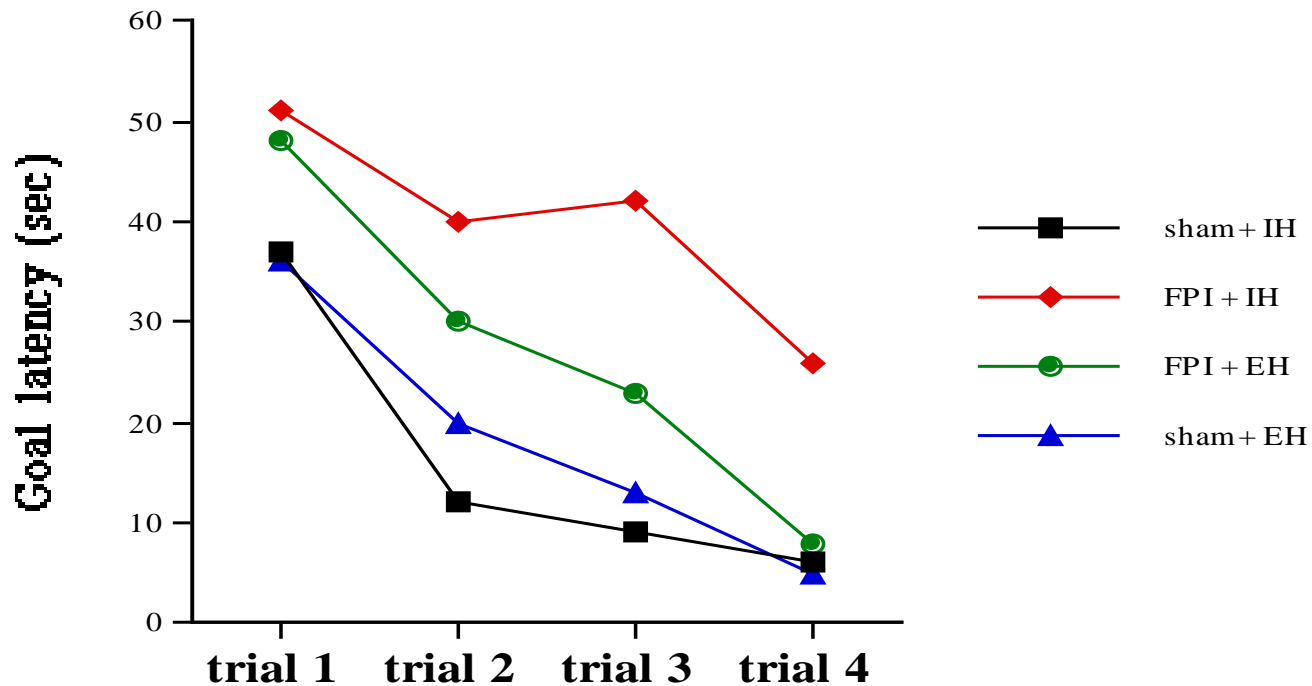


# Environmental Enrichment Increases Survival of Neural Progenitors

Nilsson et al., 1999



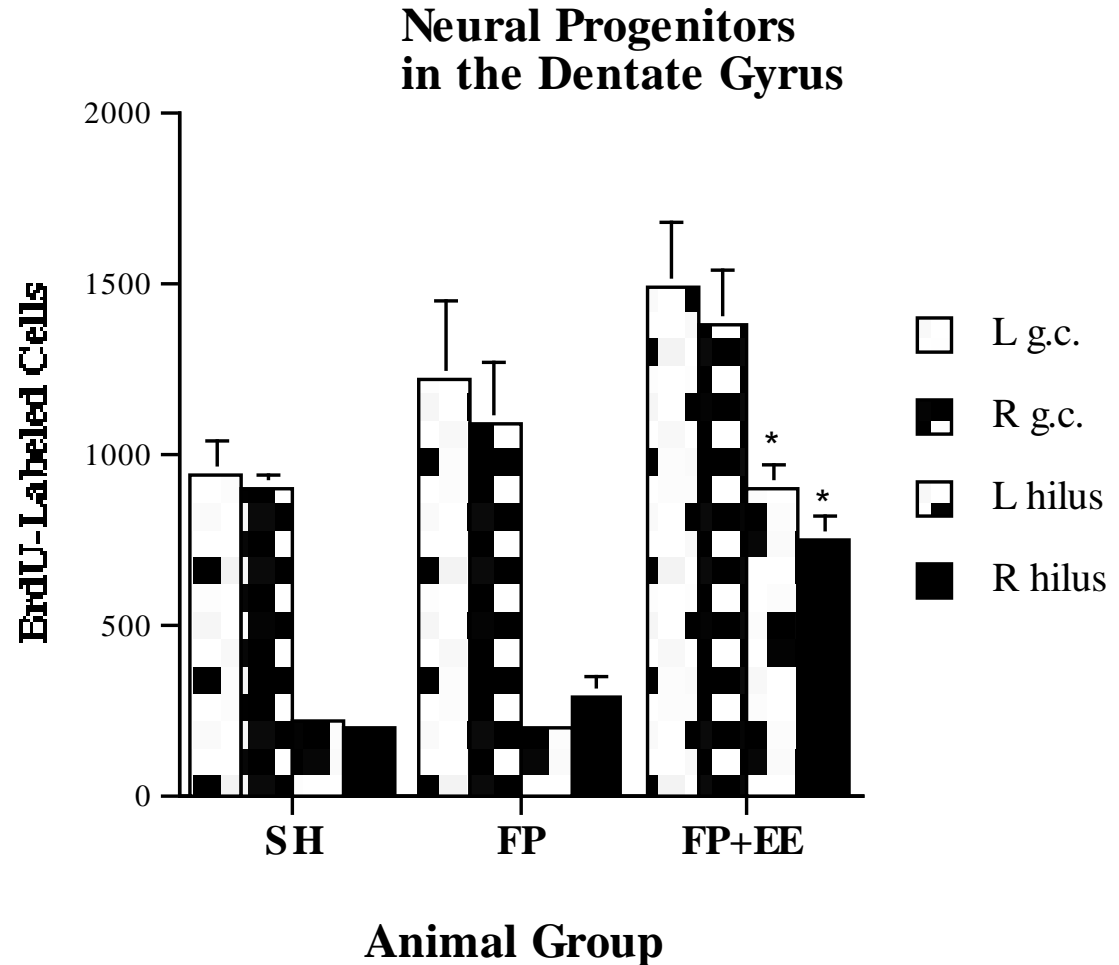
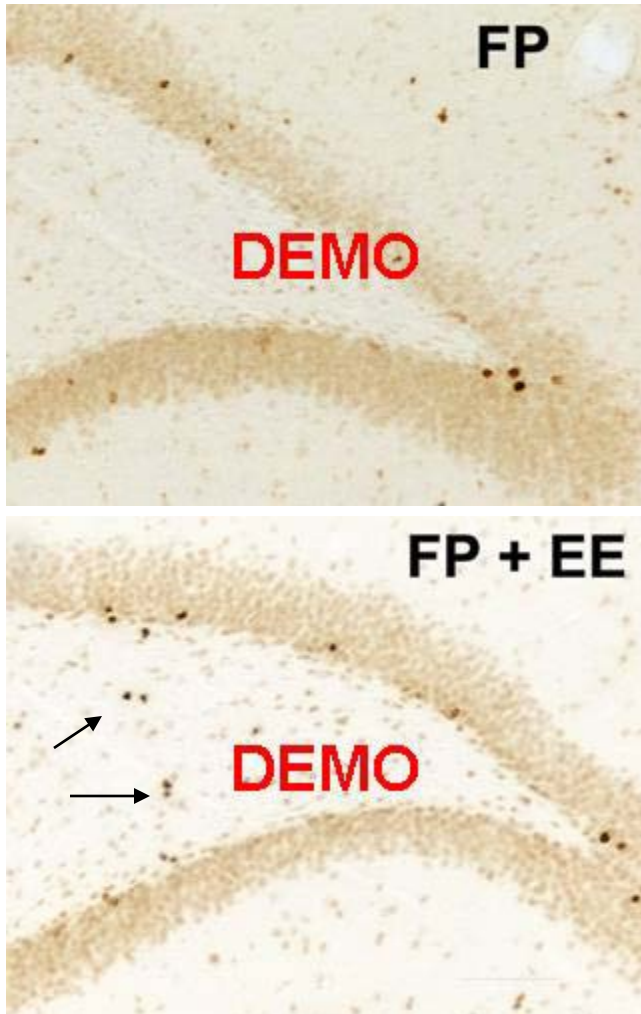
# Post-Traumatic Cognitive Deficits are Attenuated by Environmental Enrichment



*Hypothesis:*

Environmental enrichment increases survival of neural progenitors in the dentate following FP injury.

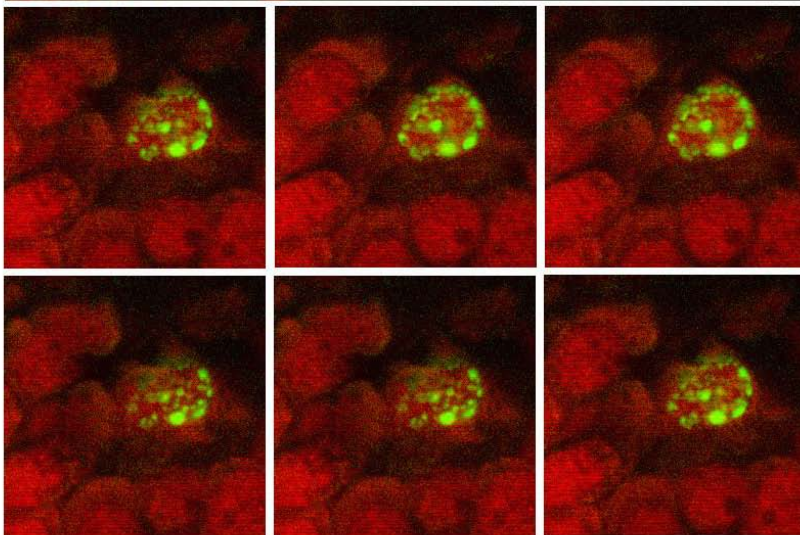
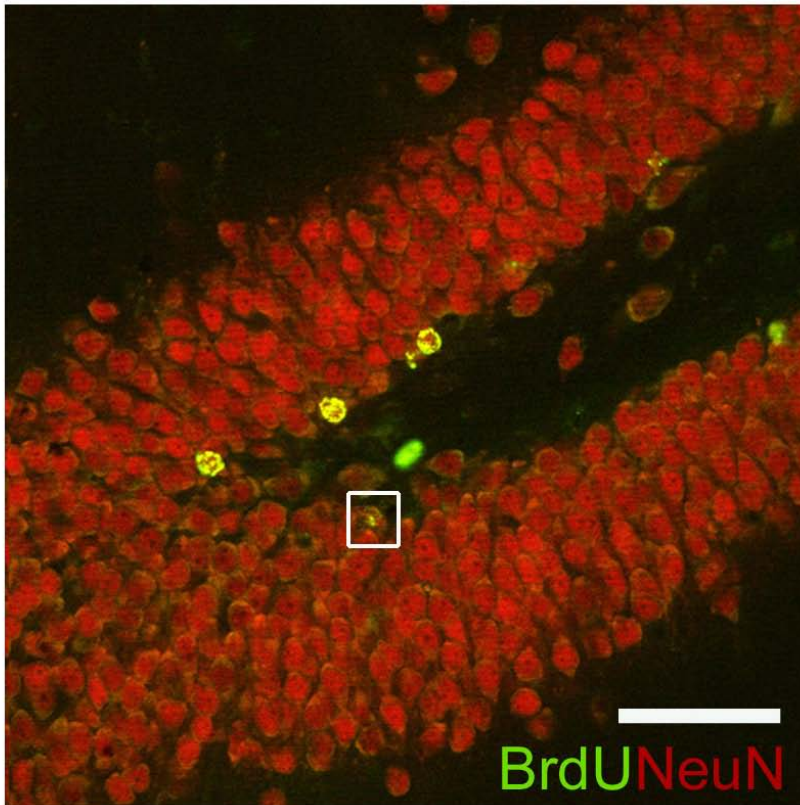
# Does Enrichment Increase Survival of Neural Progenitors in the Dentate after FP Injury?



# Why the increase in the hilus after FPI?

- Environmental niche
  - Vascular niche for adult hippocampal neurogenesis, Palmer et al., 2000
  - Neurons inhibit neurogenesis, Hastings and Gould, 2003
  - BDNF inhibits differentiation of neural progenitors after ischemia, Gustafsson et al., 2003

Are the neural  
progenitors  
neurons?



# Summary

1. Environmental enrichment increases neural progenitors in the hilus following FPI.
2. Future studies:
  - Is there a correlation between neural progenitors and learning and memory?
  - How does elimination of neural stem cells affect recovery?
  - How does timing of the intervention affect neurogenesis and recovery?
  - Do the neural progenitors make functional or aberrant connections?

# Acknowledgements

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## Physical Therapy Students

Valerie Danielson

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Valerie Delauo

# Summary and Conclusions

- Neurogenesis in adulthood is now well established
- A decrease in neurogenesis may be linked to specific deficits in cognitive function
- Factors that enhance neurogenesis may remediate these cognitive deficits
- In the future, neural stem cells may be able to replace lost cells secondary to injury and degeneration