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9.914 Special Topics: Genetics, Neurobiology, and Pathophysiology of Psychiatric Disorders
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Chronic Antidepressant Treatment Increases Neurogenesis in Adult Rat Hippocampus

Malberg, Eisch, Nestler and Duman

Journal of Neuroscience

2000

Depression and Stress

- 2-5% of the U.S. population affected
- 40-50% of the risk is genetic
- But non-genetic factors also contribute such as e.g. stress:
- Decrease in hippocampal volume associated with depression and stress
 - reduced hippocampal granule cells genesis
 - decreased cell proliferation
 - death of CA3 pyramidal neurons

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- But non-genetic factors also contribute such as e.g. stress:
- Decrease in hippocampal volume in patients with depression and stress
 - **reduced hippocampal granule cells genesis**

Does antidepressant treatment influence adult neurogenesis in the hippocampus?

Neurogenesis in the Adult Brain

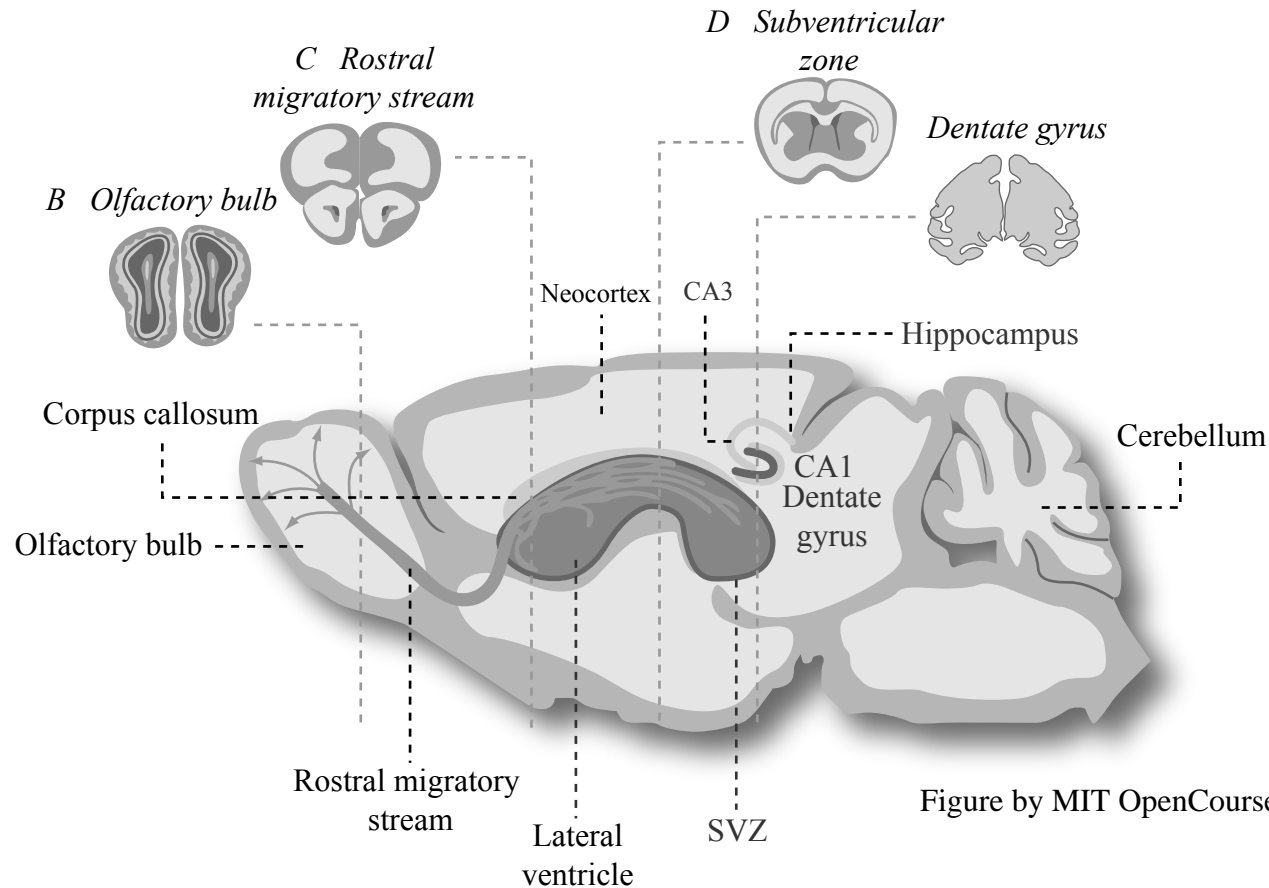


Figure by MIT OpenCourseWare.

Neurogenic Niche:

Microenvironment that allows differentiation and integration of newborn neurons

(diffusible molecules, influence of neighboring cells or neurons that are connected to these, neurotransmitter levels, synaptic contacts...)

Subventricular Zone (SVZ)

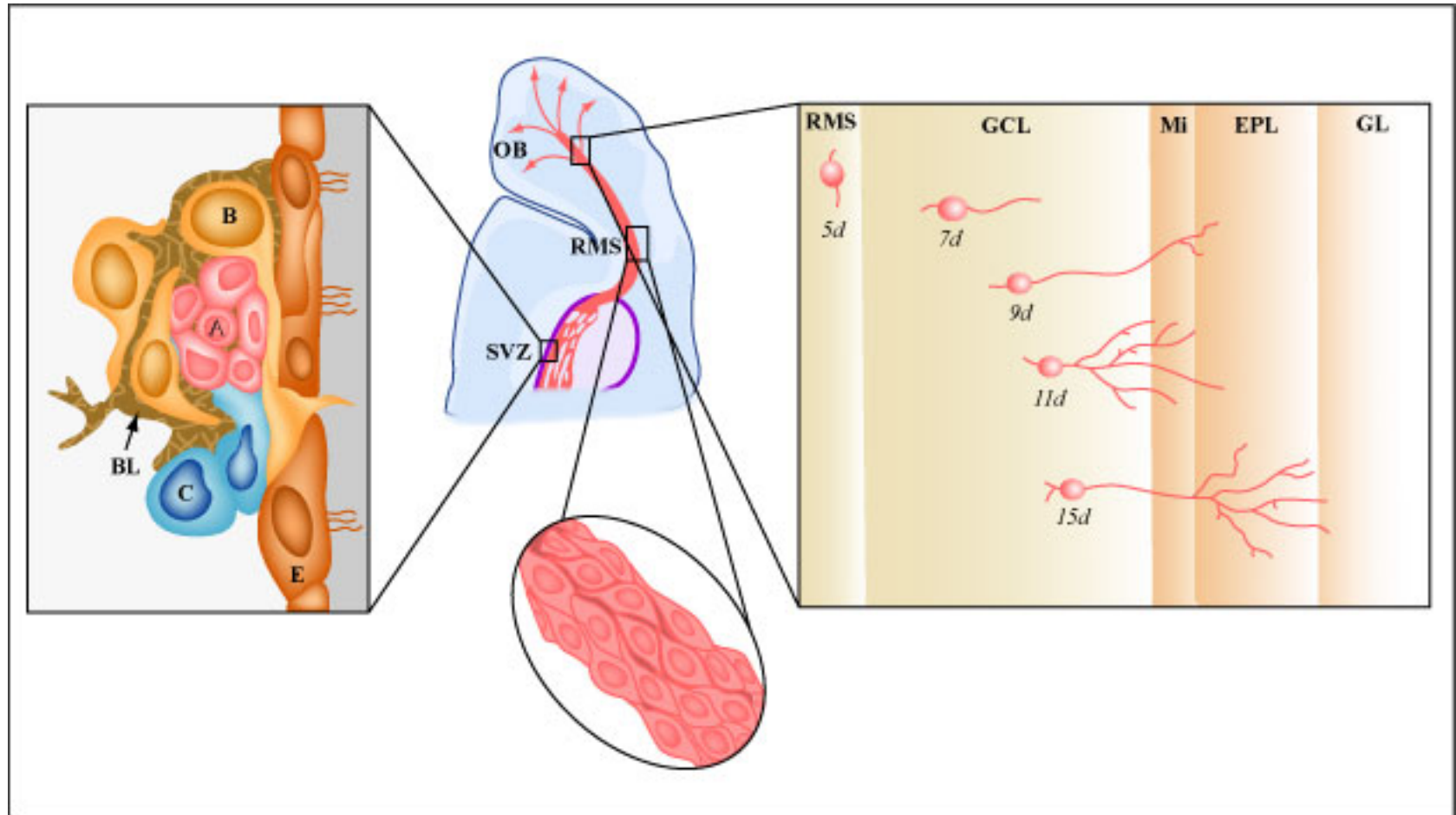


Figure by MIT OpenCourseWare.

Subgranular Zone (SGZ)

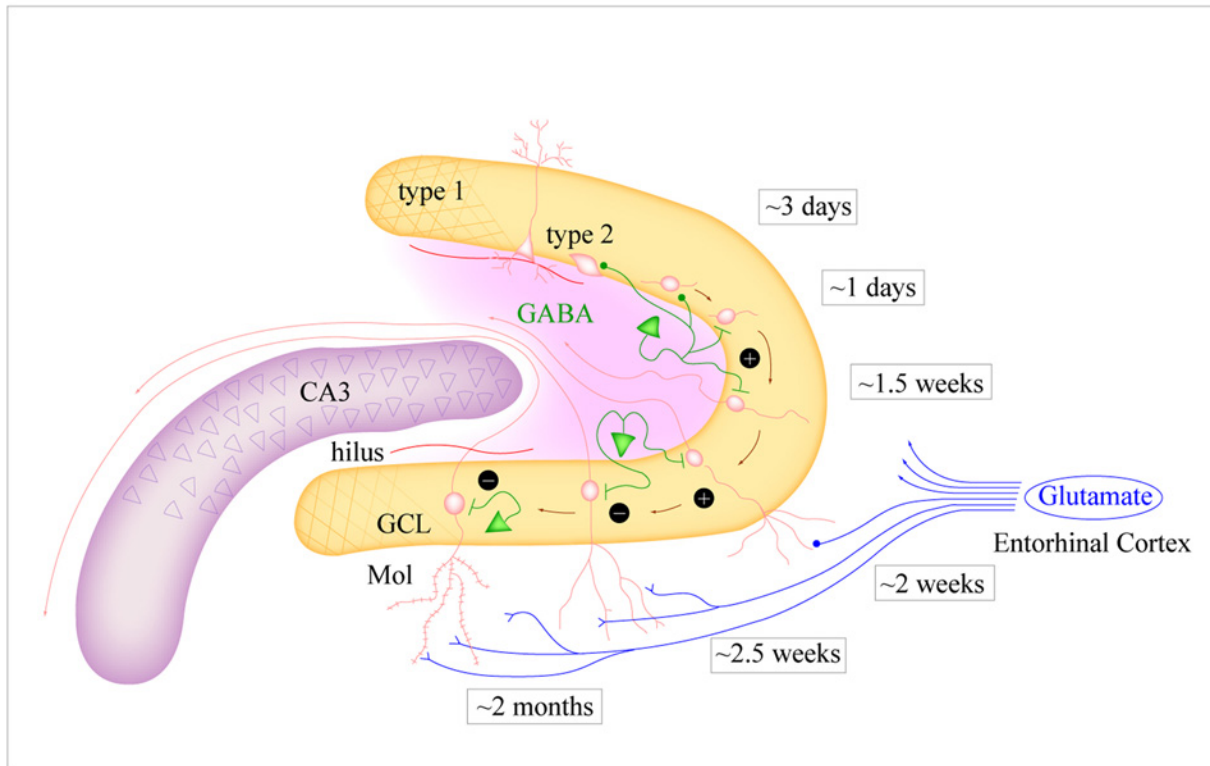


Figure by MIT OpenCourseWare.

Chronic Antidepressant Treatment Increases Neurogenesis in Adult Rat Hippocampus

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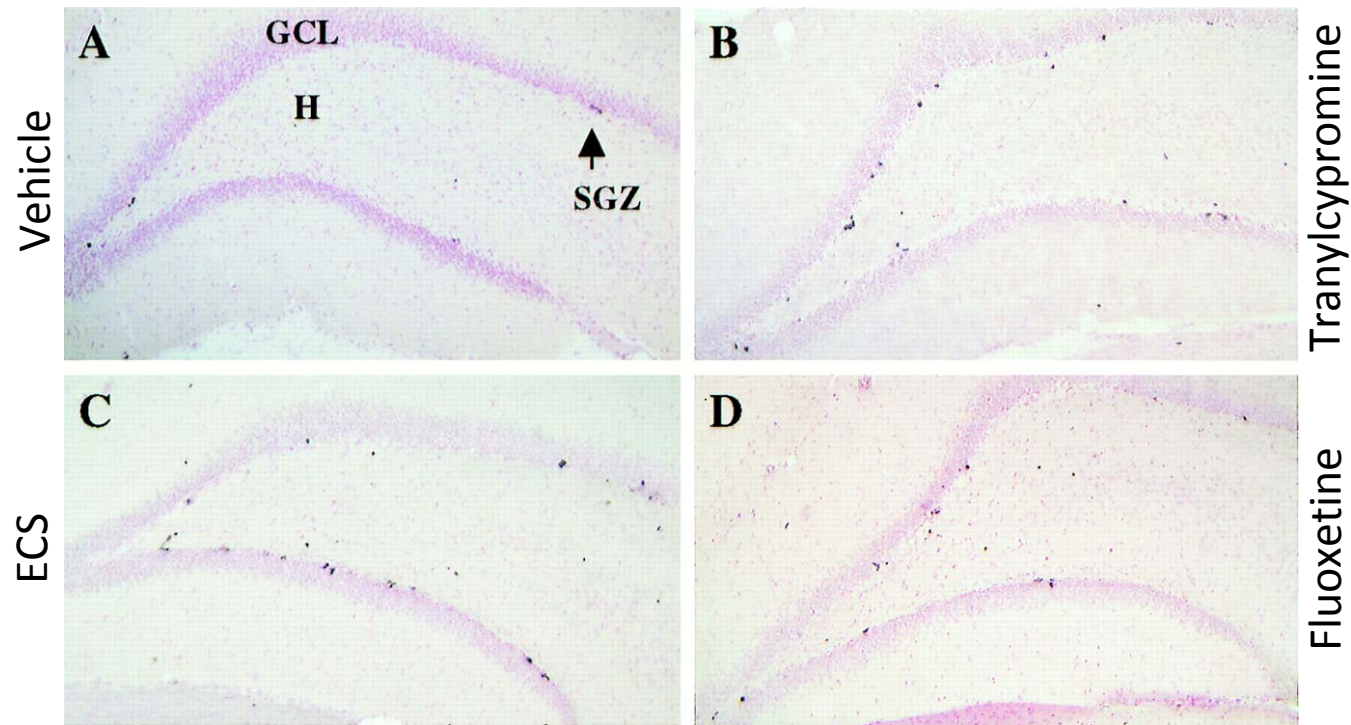
Bromodeoxyuridine (BrdU)

- Used as thymidine analog
- Incorporates into the DNA during S-phase
- Can be visualized using a BrdU antibody

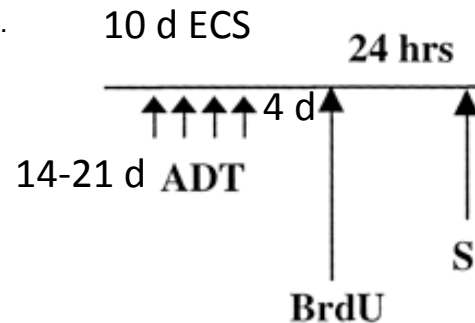
But keep in mind:

- Does NOT label proliferation but DNA synthesis
→ appropriate controls (for example DNA repair)
- Toxic, mutagenic substance (cell death, alters NA stability, influences cell cycle...)

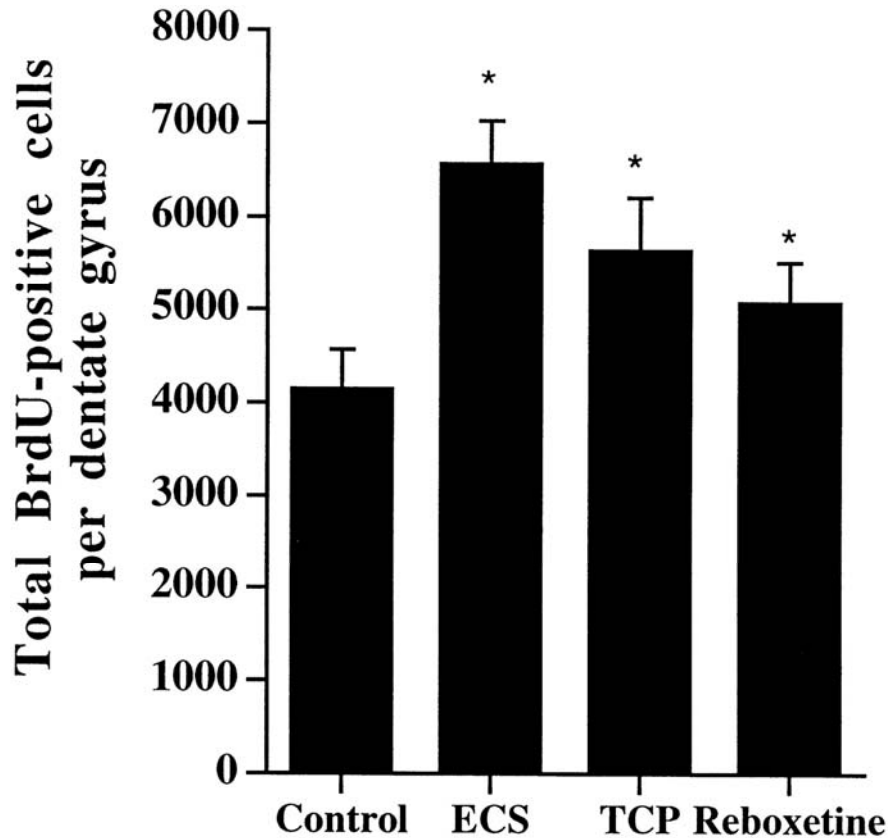
1) Does chronic antidepressant treatment increase number of BrdU positive cells?



Courtesy of Society for Neuroscience. Used with permission.



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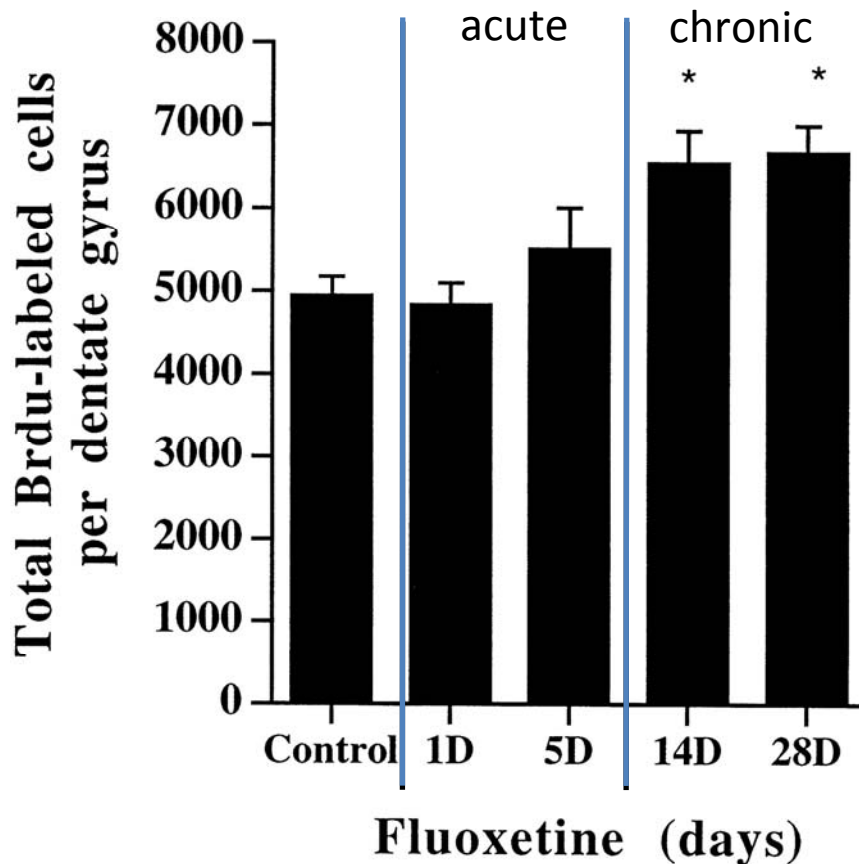
- ECS: 50% increase
- Chemical antidepressants: 20-40% increase

In general:

- dosage of chemical antidepressants used seems to be relatively high
- Count cells in hilus and SGZ

Is this an effect of chronic treatment or can it also be achieved by acute treatment?

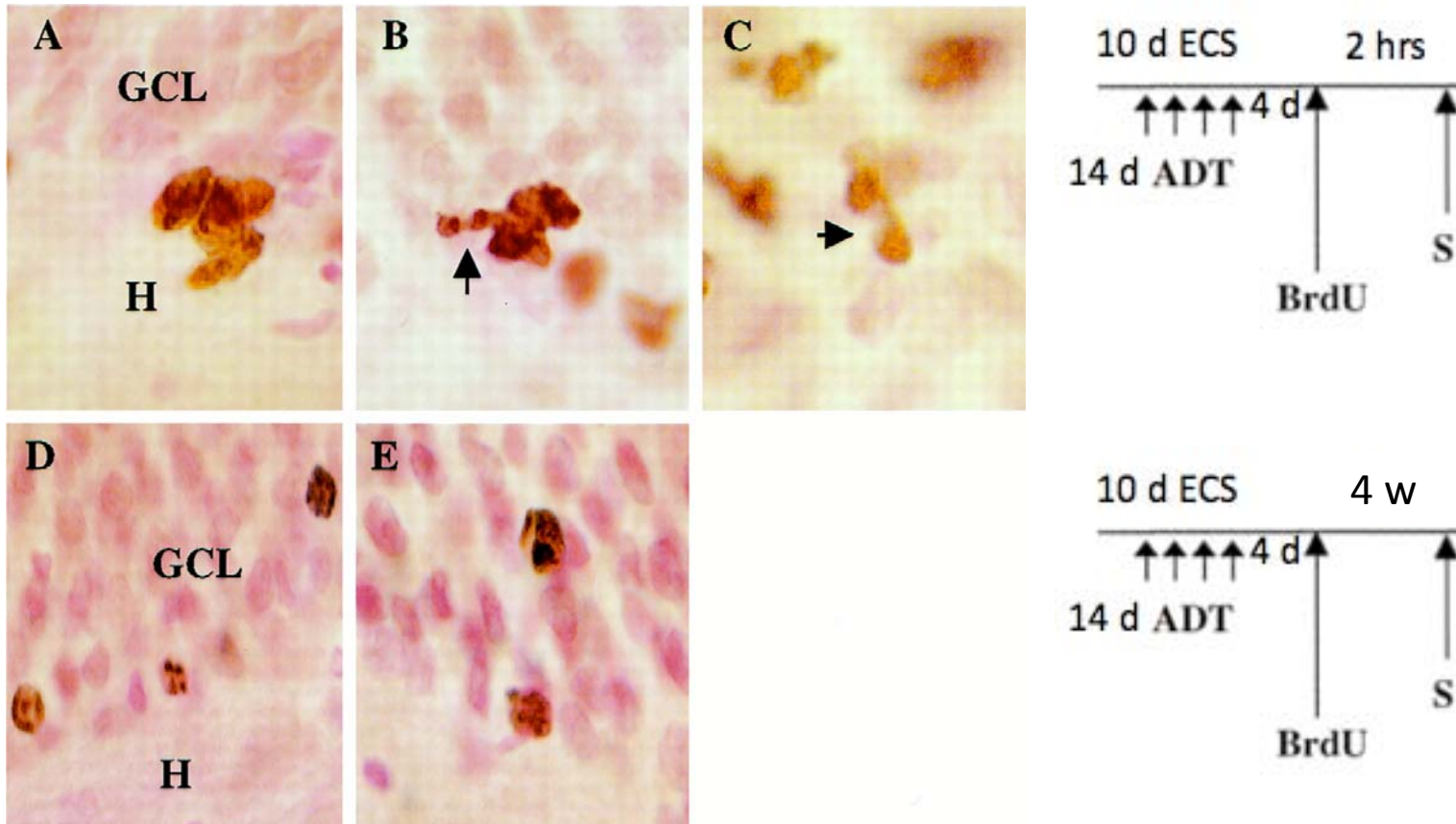
1) Does chronic antidepressant treatment increase number of BrdU positive cells?



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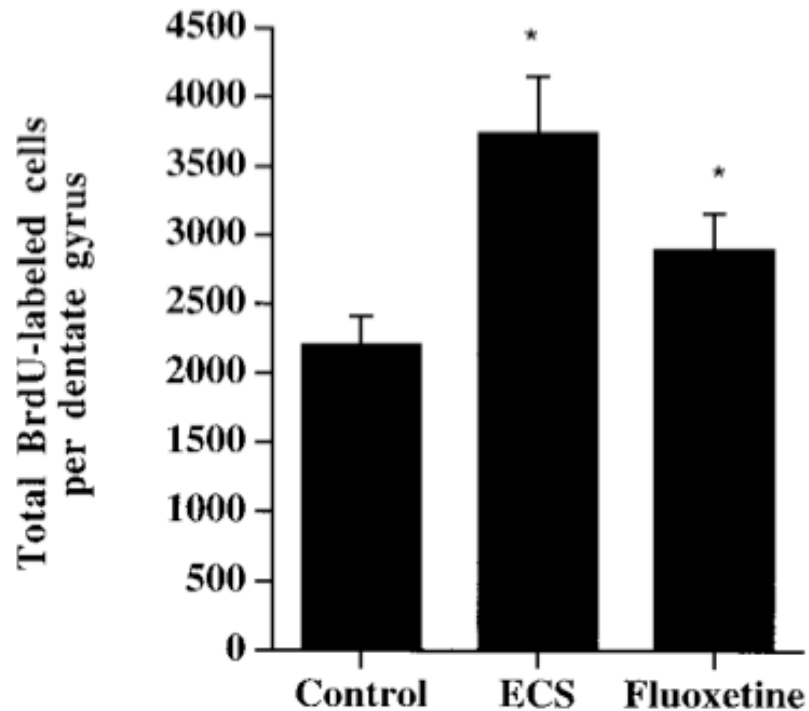
- Acute treatment does not affect BrdU-positive cell number
 - Long-term treatment leads to a significant increase
 - Not seen with non-antidepressant psychotropic drug (haloperidol)
 - Consistent with time course for therapeutic action
- Onset of Fluoxetine 4-6 weeks (dosage dependent?)

2) Does chronic treatment increase cell proliferation?



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3) Are the new cells surviving and is treatment influencing survival rate?

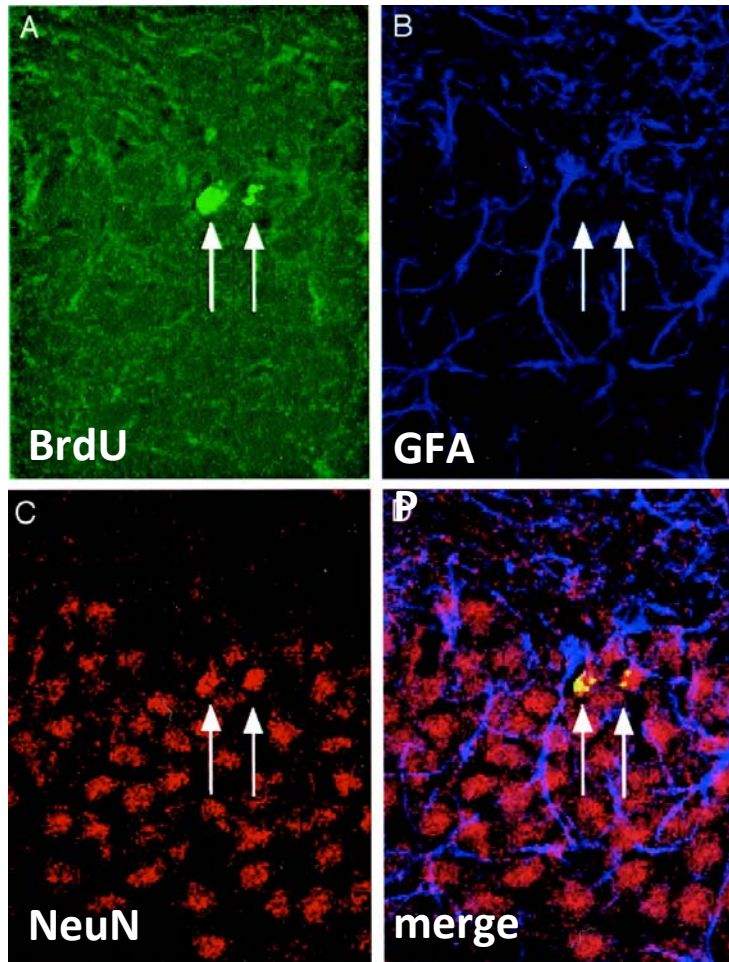


Courtesy of Society for Neuroscience. Used with permission.

- Total number of BrdU labeled cells is decreased both in control and in treated group
- Treatment does not influence survival

Do these cells differentiate?
Is there an influence on cell fate?

4) What are the cell fates of the newborn cells?



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After 4 weeks:

- no clusters

In both control and treated groups:

- 75% neuronal
- 13% non-glial
- 12% not labeled with either marker

→ Antidepressants do not influence differentiation

→ Antidepressants do not influence survival and maturation

Summary

Chronic antidepressant treatment increases neurogenesis in the dentate gyrus

Treatment:

- increases cell proliferation (increase in BrdU labeled cells)
- does not influence cell survival
- does not influence cell differentiation

Discussion

- Is SGZ neurogenesis necessary for antidepressant function? (Simona)
- Neurogenesis by itself not enough but cells need to be integrated into circuitry (behavioral effect? Simona)
- How do the antidepressants influence neurogenesis? (microenvironment of SVZ but also influence of other brain regions) (Simona)
- Effects are influenced by genetic background of animal
- How does this translate into humans? (reduced volume due to reduced neurogenesis?)
- How does hippocampal neurogenesis contribute to regulation of emotion? (differences between ventral and dorsal hippocampus)