Adult Neurogenesis

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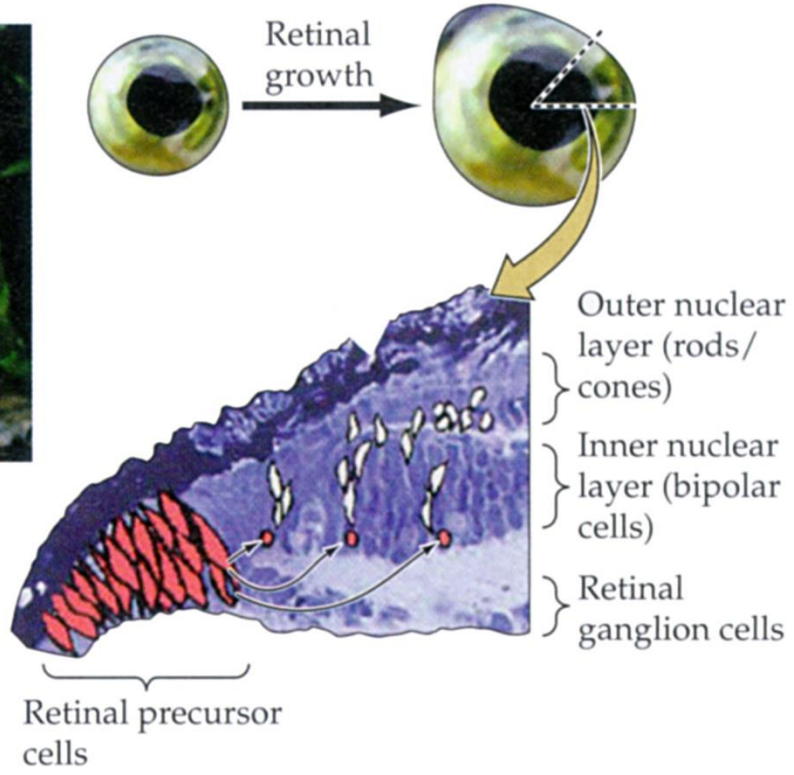
Death of a Dogma

“Once development has ended, the fonts of growth of the cells, axons and dendrites dries up irrevocably. In adult centers, the nerve paths are fixed and immutable: everything may die, nothing may be regenerated.”

Santiago Ramon y Cajal, 1928

Cold Blooded Species

- Teleost fish (e.g. goldfish) grow throughout life.
- The nervous system grows in proportion to the rest of the body.
- New neurons, including those with long projecting axons, grow axons and dendrites and form synaptic connections. New neurons integrate with the existing system.



Cold Blooded Species

- Amphibians and certain other cold blooded species can regenerate much of the nervous system following trauma.

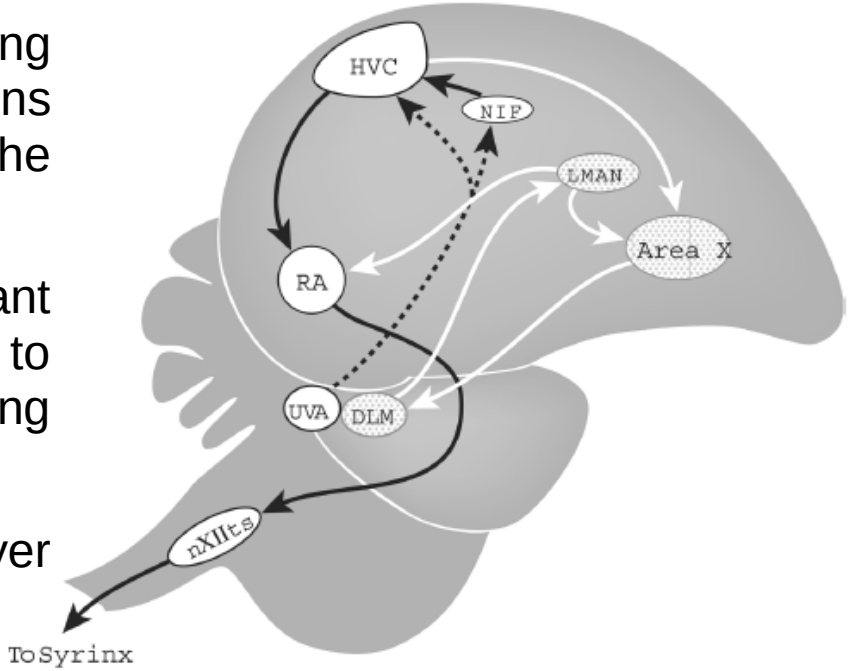
Warm Blooded Species

Warm blooded species …

- have neurogenesis in only a few specific cell groups in the adult.
- do NOT exhibit an ability for large scale regeneration of neurons.

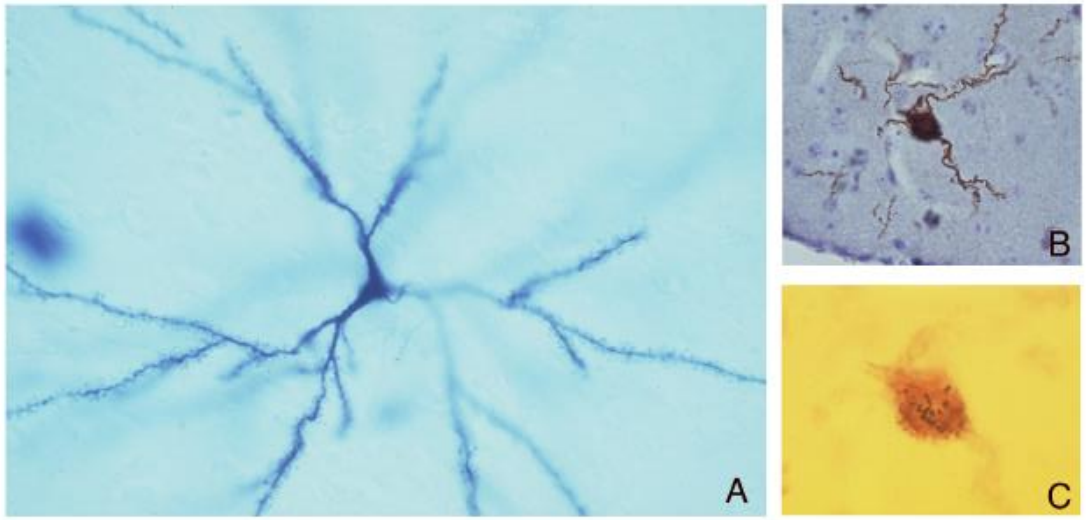
Song Birds

- Canaries, sparrows and other migrating songbirds generate many of the neurons in the song centers of the brain in the spring.
- Males show the most significant neurogenesis, which is in response to androgens. Also, males sing the mating song.
- Cells are generated in the ventricular layer of the forebrain.
- New cells migrate along radial glia to the song nuclei, including the high vocal center (HVC), robustus of the archistriatum (RA) and area X.



Song Birds

- New neurons grow axons and dendrites, form synaptic connections and are functional.
- At the end of the mating season, many of the cells in the song centers of the brain die.



1. tritiated thymidine injection into adult male canary
2. (4 weeks later) electrophysiological recording in HVC followed by filling the recorded neurons by horse radish peroxidase (HRP)
3. sacrifice and stain for HRP (A, B) and autoradiography for tritiated thymidine (C).

About 1 out of 10 filled neurons were positive for thymidine incorporation.

Mammals

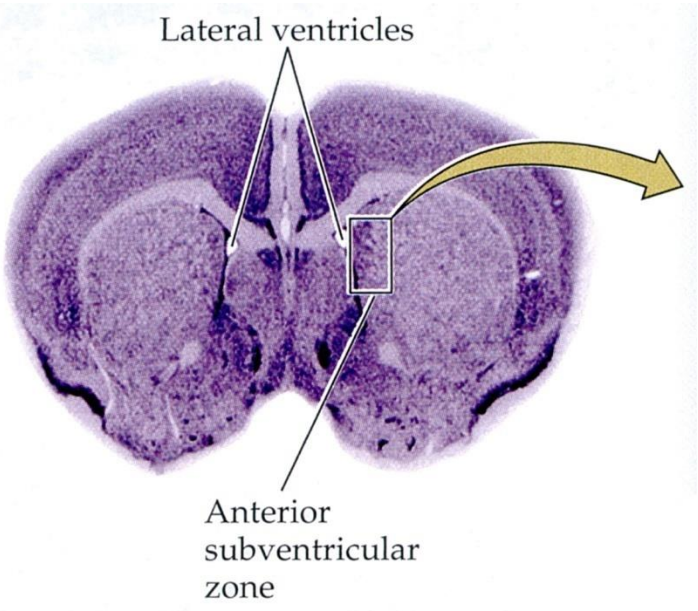
- The dogma for almost 100 years was that no new neurons are generated in the adult mammalian brain.
- In the 1960s & 70s, there were reports of cells that looked like neurons in a few locations in the adult brain that were labeled following injections of ^{3}H-thymidine.

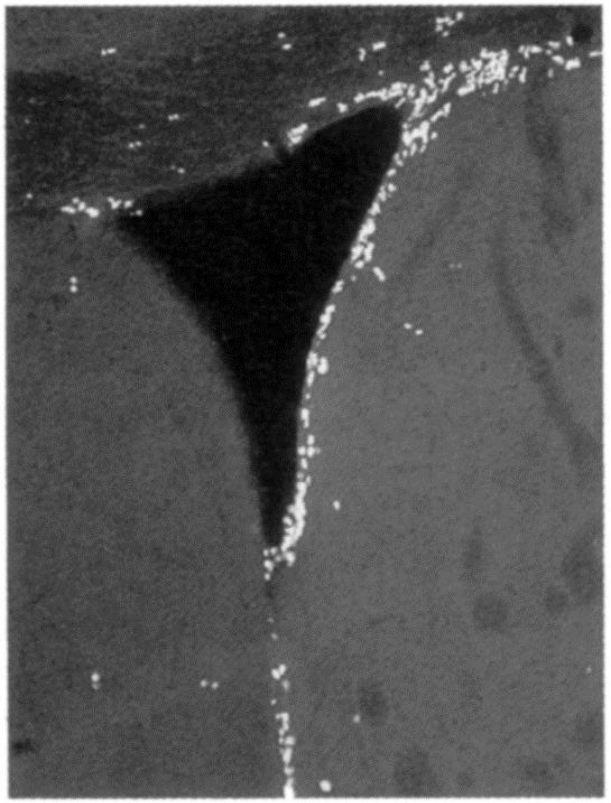
  These reports were mostly discounted.
- Over the past 25 years, neurogenesis has been definitively identified in two locations in the adult mammalian brain (including humans)…SVZ and SGZ.

Subventricular Zone (SVZ)

- New neurons and astrocytes are generated in the subventricular zone (SVZ) adjacent to the lateral ventricle in the forebrain.

  They can be labeled with BrdU or ^{3}H-Thymidine, and the new cells express neuronal or glial markers.

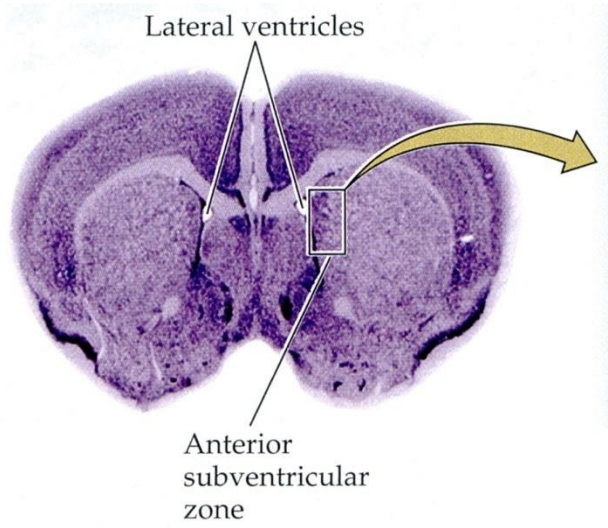


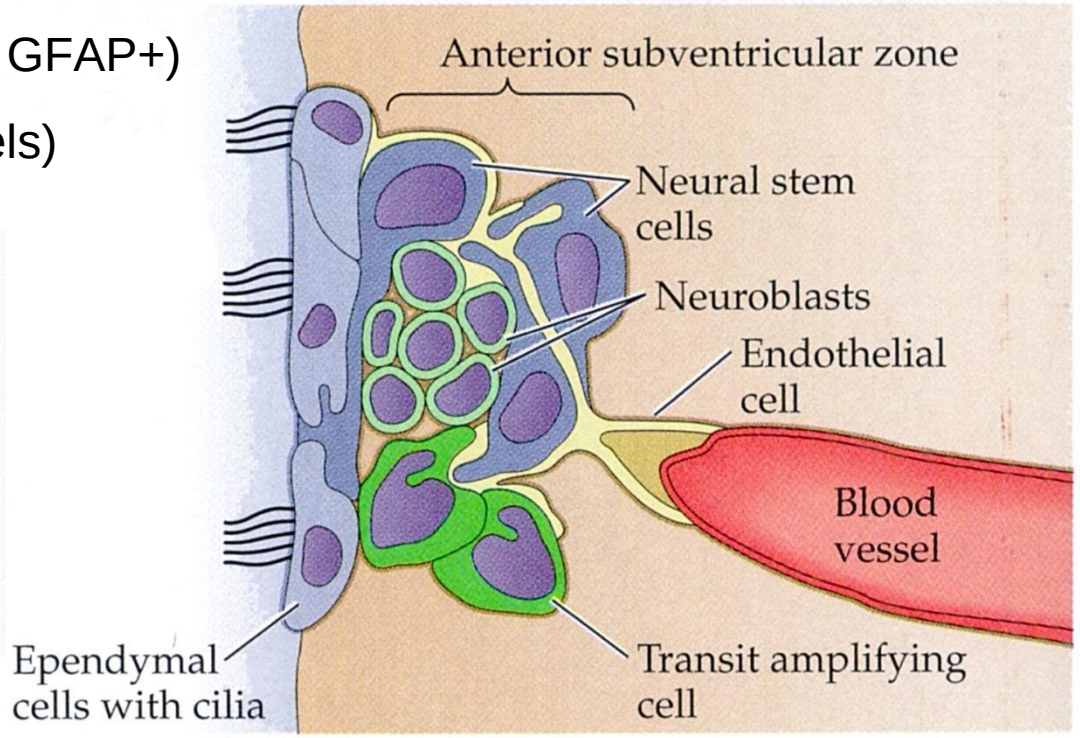


subventricular zone

Subventricular Zone (SVZ)

- Six types of cells in the SVZ:
- ependymal cells
- neural stem cells (B cells)
- transit amplifying cells (C cells)
- neuroblasts & glioblasts (A cells)
- astrocytes (multipolar shape, GFAP+)
- endothelial cells (blood vessels)





Subventricular Zone (SVZ)

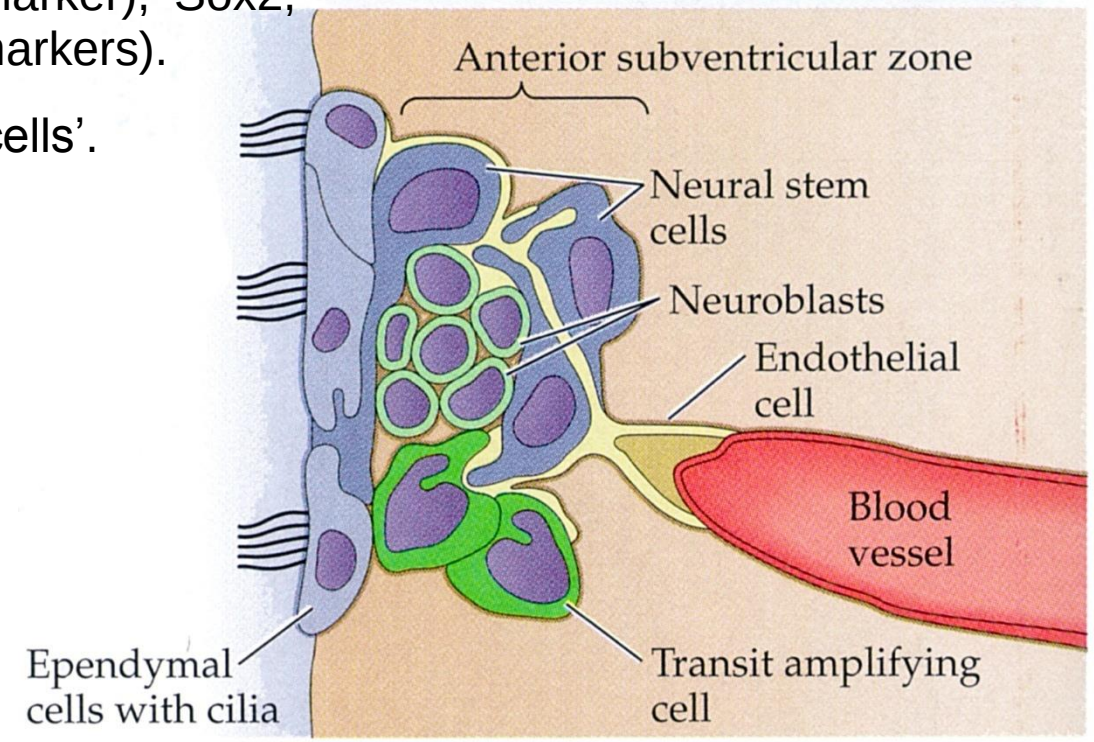
- Neural stem cells (B cells) …

- are self replicating and multipotent (i.e. give rise to multiple cell types), so they meet the definition of a ‘stem cell’.

- divide very slowly.

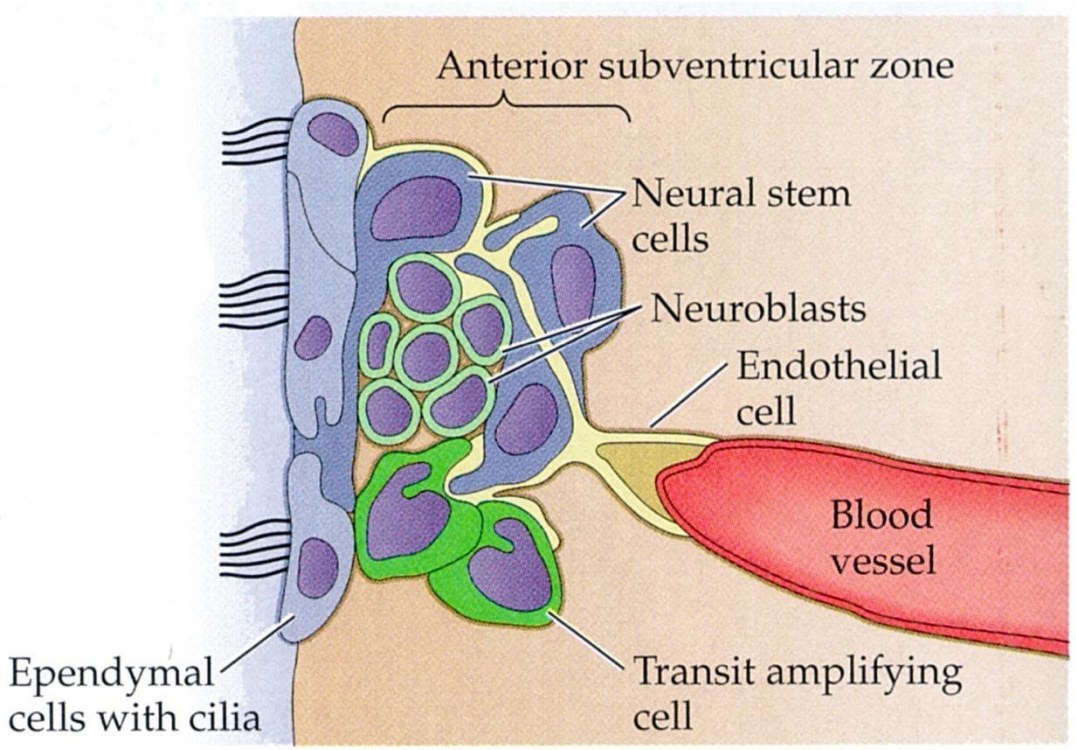
- express GFAP (astrocyte marker), Sox2, and Nestin (progenitor cell markers).

- generate ‘transit amplifying cells’.



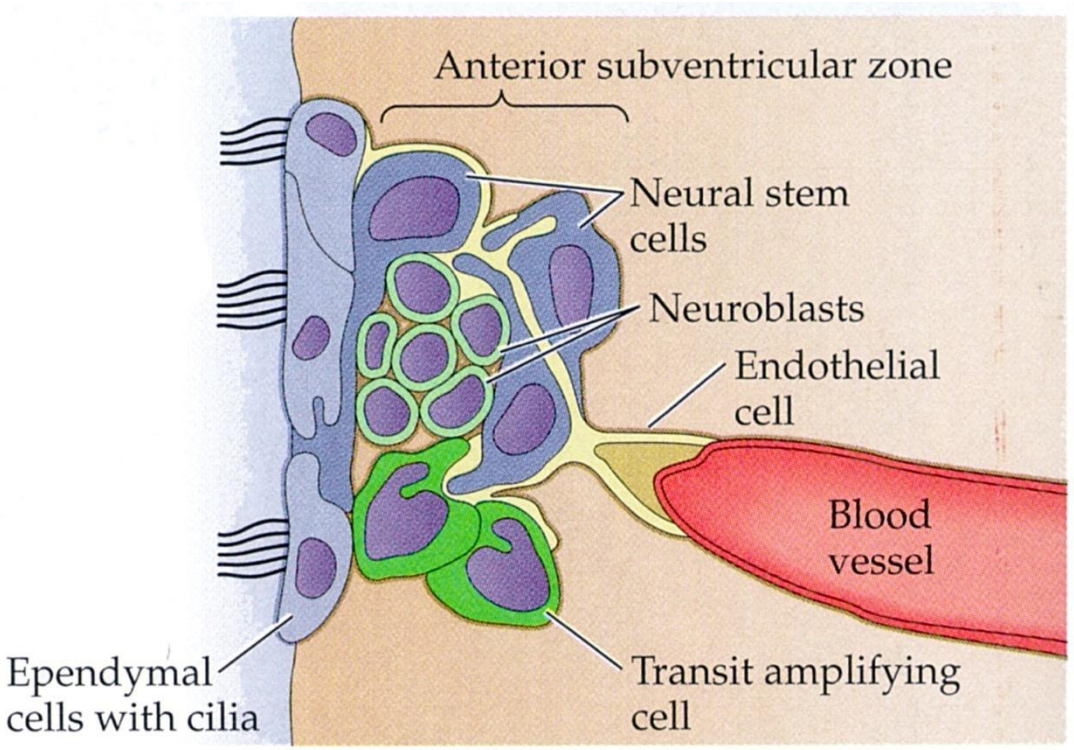
Subventricular Zone (SVZ)

- Transit amplifying cells (C cells) …
- divide rapidly.
- express Sox2, Nestin (not GFAP).
- generate ‘neuroblasts’ and ‘glioblasts’.
- are capable of only a few divisions.



Subventricular Zone (SVZ)

- Neuroblasts and glioblasts …
- are newly postmitotic, differentiating cells. (i.e. They do not divide.)
- express markers of differentiating cells; neuroblasts express Doublecortin until they begin to express neurotransmitter near the end of migration.



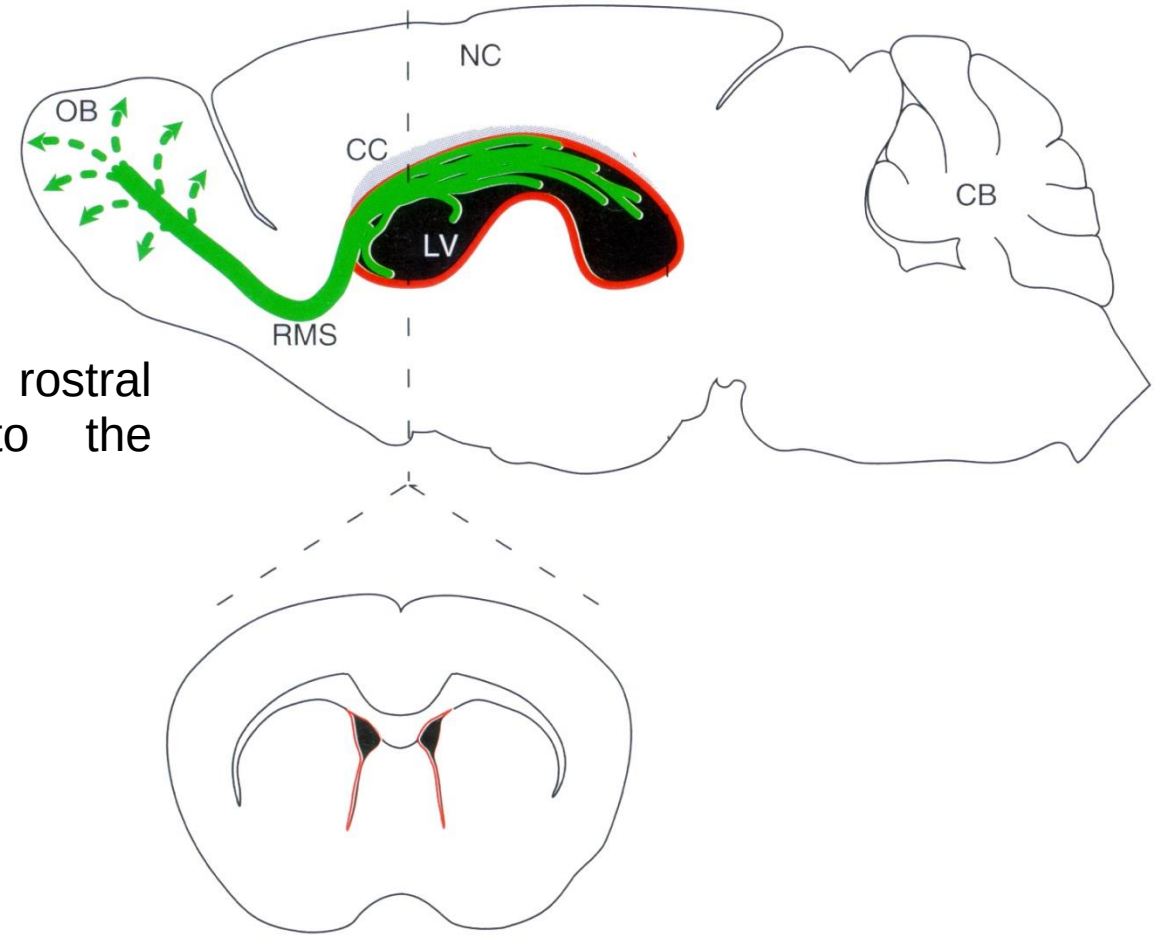
Subventricular Zone (SVZ)

- If rapidly dividing cells are killed with cytosine arabinoside, then the transit amplifying cells are lost, but begin to reappear after several days.
- No neuroblasts or glioblasts develop without transit amplifying cells.

neural stem cell →	transit amplifying cell	→ neuroblast
B cell	C cell	A cell
slowly dividing	fast dividing	non dividing migrating
GFAP+ Sox2+ Nestin+	Sox2+ Nestin+	Doublecortin+ NeuN+ Neurofilament+

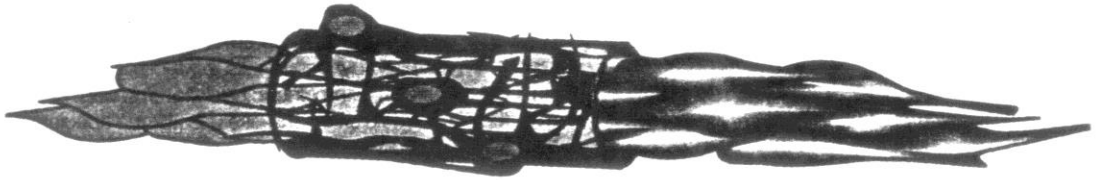
Subventricular Zone (SVZ)

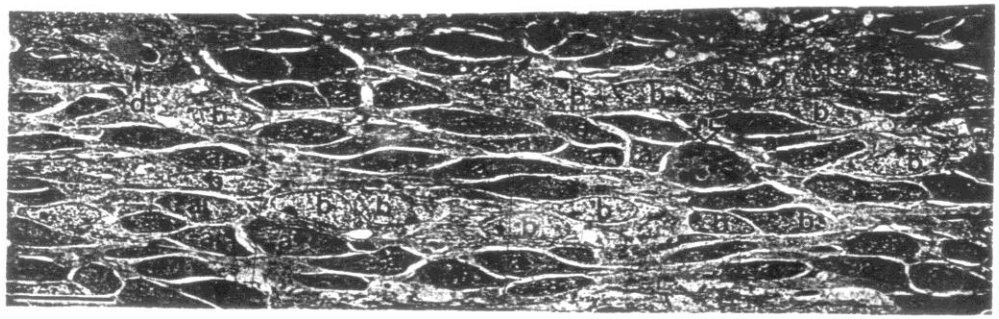
- Neuroblasts migrate in the rostral migratory stream (RMS) to the olfactory bulb.



Subventricular Zone (SVZ)

- The RMS is a tube bounded by astrocytes.
- Cells migrate by leap-frogging along one another. N-CAM mediates cell-cell adhesion.
- Laminin is expressed in the RMS, and migrating cells express a laminin binding integrin, α1β1.
- Netrin-1 is expressed by mitral cells in the olfactory bulb, and the netrin-1 gradient attracts migrating cells.
- Slit is expressed by the septum and surrounding areas, and it repels migrating olfactory cells from the SVZ.





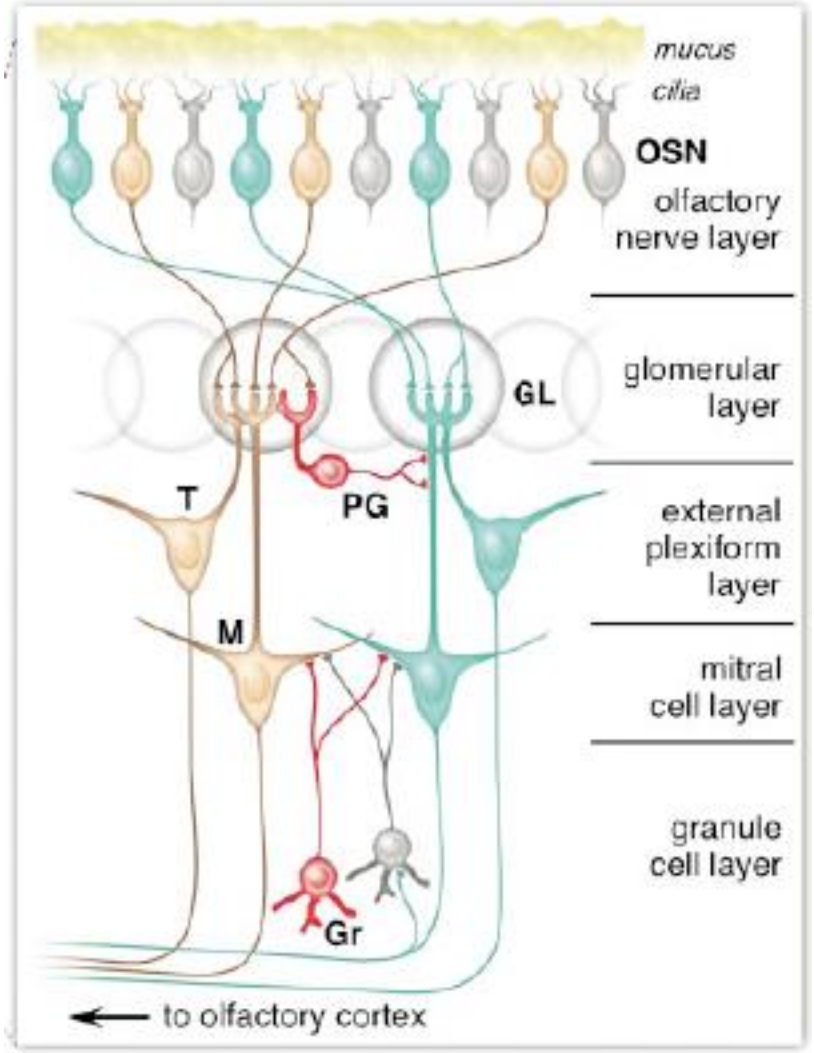
Subventricular Zone (SVZ)

- Many of the new neurons die.
- Some of the new neurons integrate into the existing circuitry and function.
- The new neurons differentiate into multiple types of interneurons.
- No neurons with long projecting axons are generated.

Subventricular Zone (SVZ)

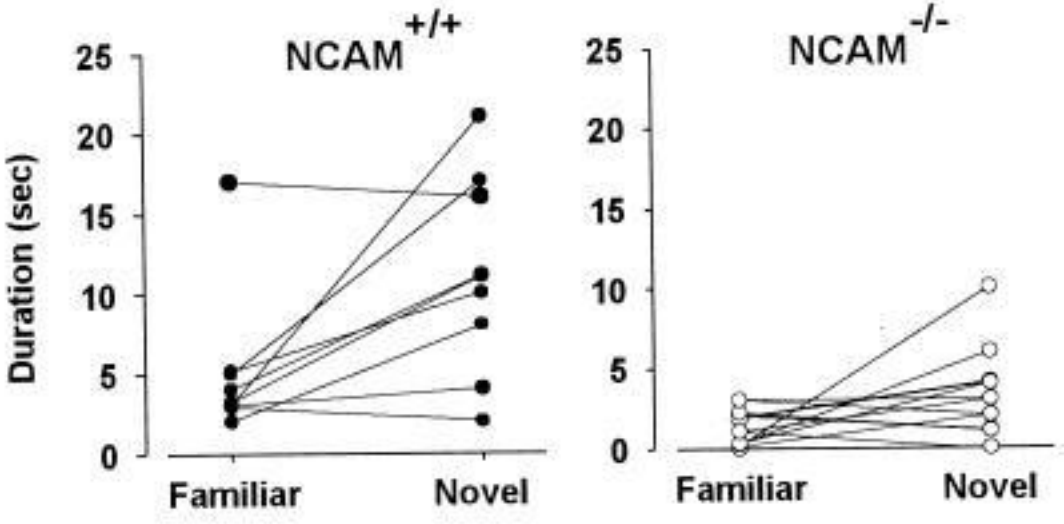
New neurons differentiate into multiple types of interneurons in the olfactory bulb:

- Periglomerular cells
  - GABA+ / Calbindin+
  - GABA+ / Calretinin+
  - GABA+ / Dopamine+
  - Glutamine
- Granule Cells
  - GABA+ / Calretinin+



Subventricular Zone (SVZ)

- Blocking migration of new olfactory bulb interneurons resulted in impairment in odor discrimination in mice.



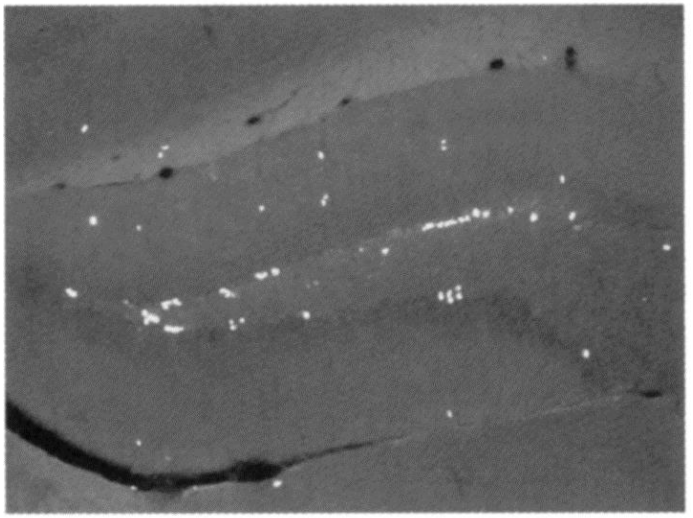
Subventricular Zone (SVZ)

- There is no net growth of the olfactory bulb.
  (i.e. Neurons must also continually die.)

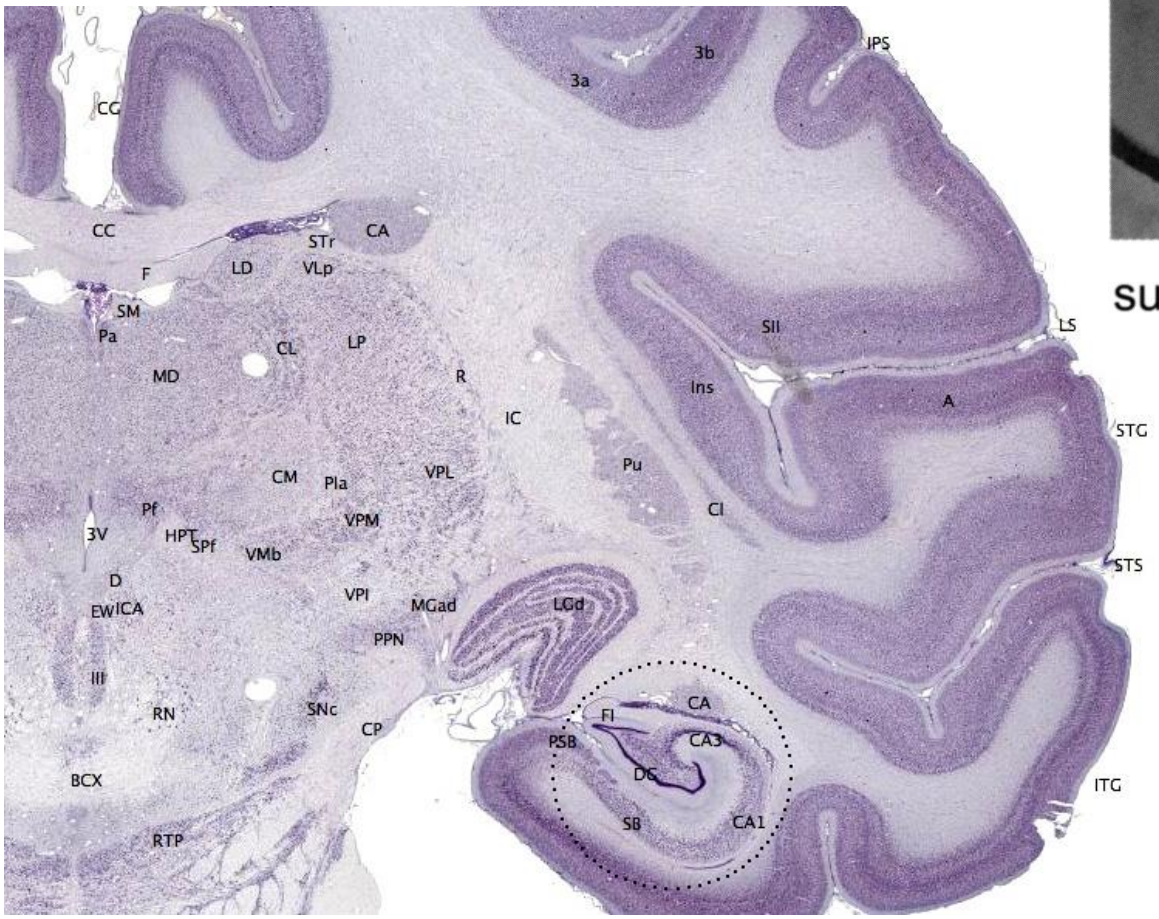
- In humans, neurogenesis in the SVZ is believed to end early in life.

Subgranule Zone (SGZ)

- Neurons and glia are generated just below the granule cell layer in the dentate gyrus of the hippocampus.

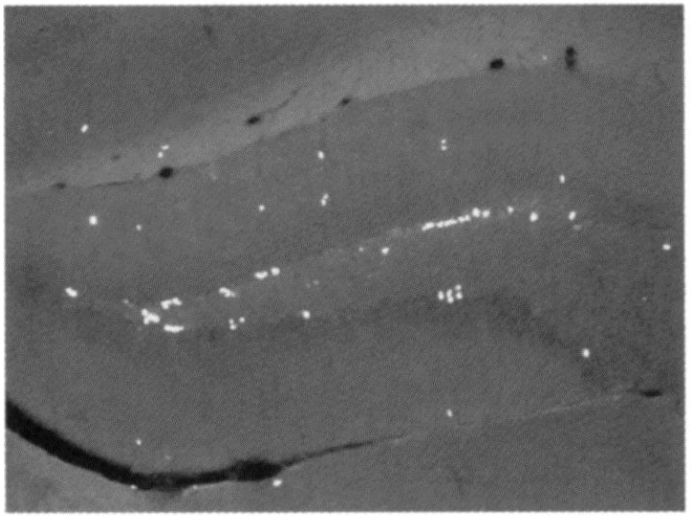


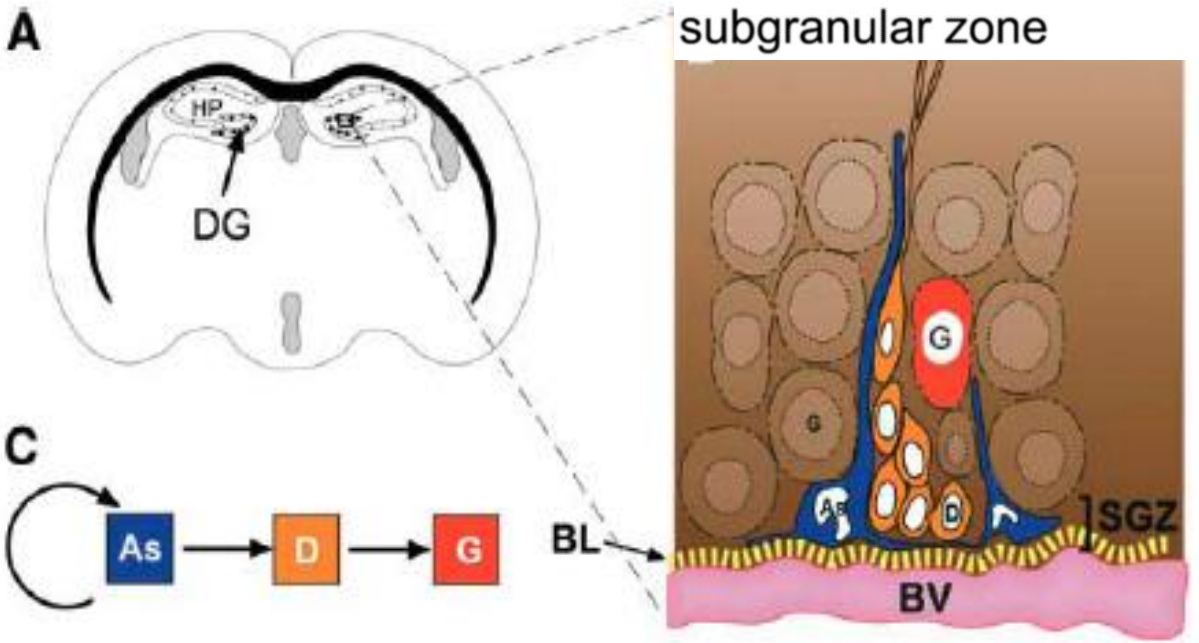
subgranular zone



Subgranule Zone (SGZ)

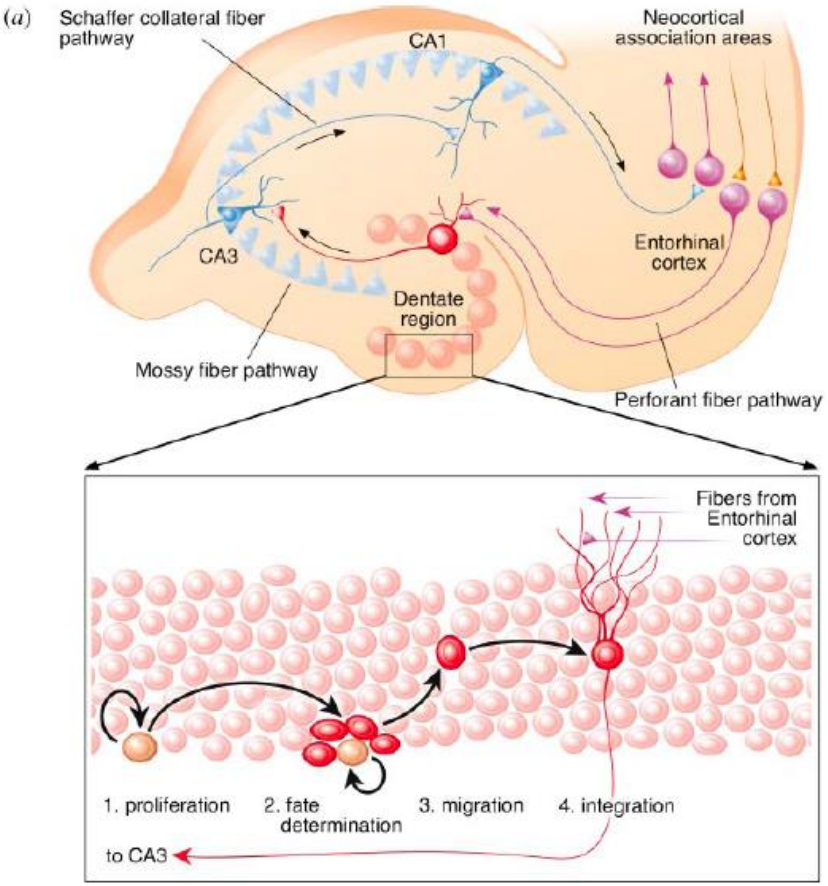
- Neurons and glia are generated just below the granule cell layer in the dentate gyrus of the hippocampus.
- Same cell types as in SVZ.
- ~700 cells are generated per day.





Subgranule Zone (SGZ)

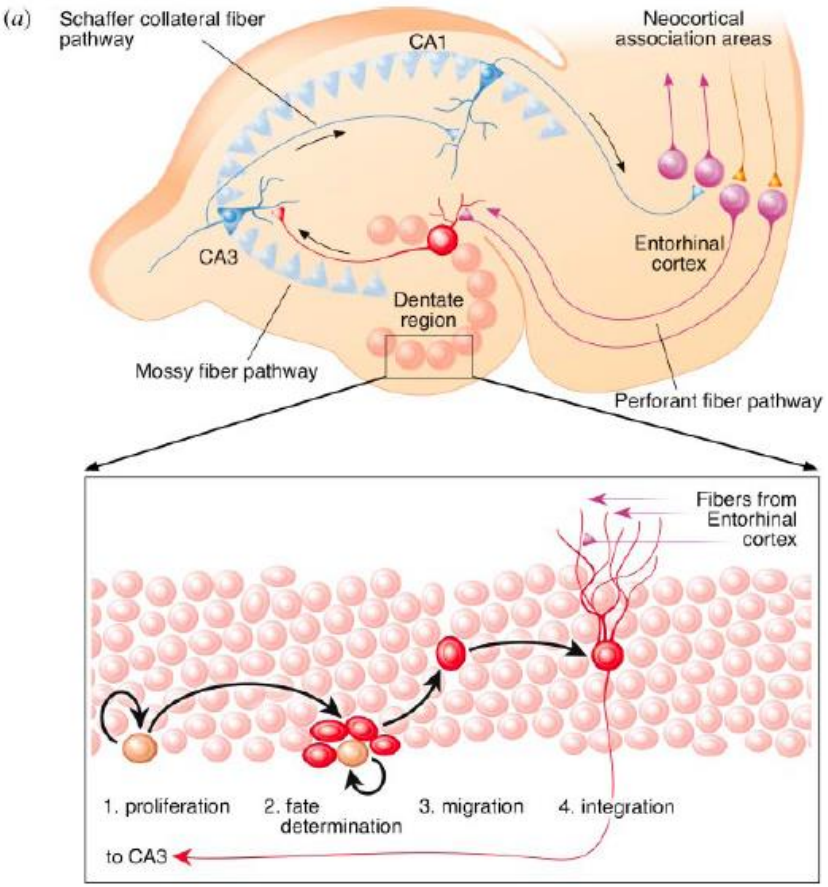
- Cells migrate the short distance from the SGZ into the granule cell layer of the dentate gyrus.
- Most new neurons die.
- Some new neurons integrate and have adult granule cell properties 4-8 weeks after terminal division.
- ~2% of the granule cells are replaced per year.



Subgranule Zone (SGZ)

- New neurons can be activated by stimulation of the perforant path, a major input to the dentate gyrus.
  (i.e. the new neurons function)

- New neurons send axons to the CA3 subregion of hippocampus via the mossy fiber tract.

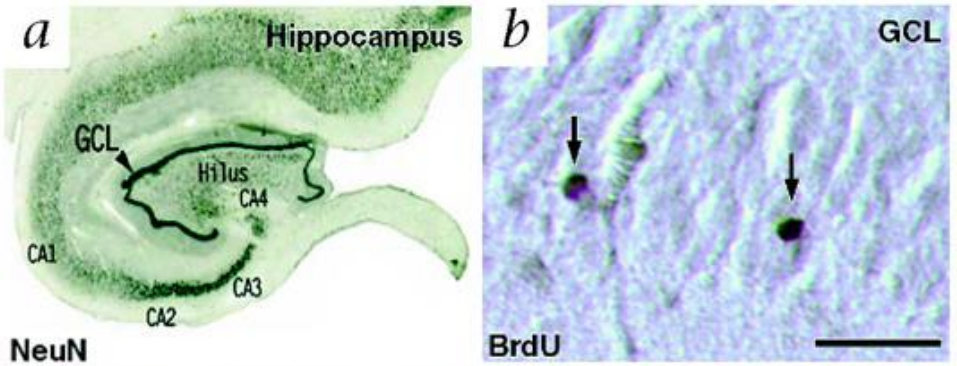


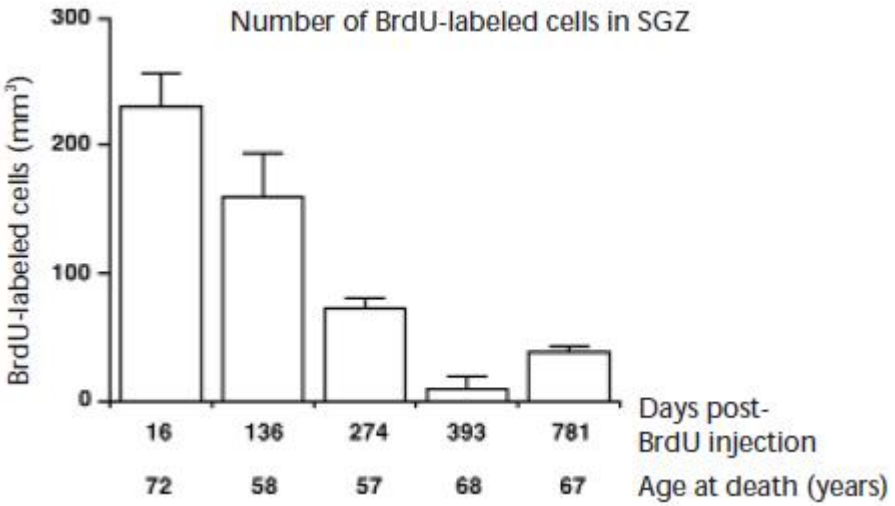
Subgranule Zone (SGZ)

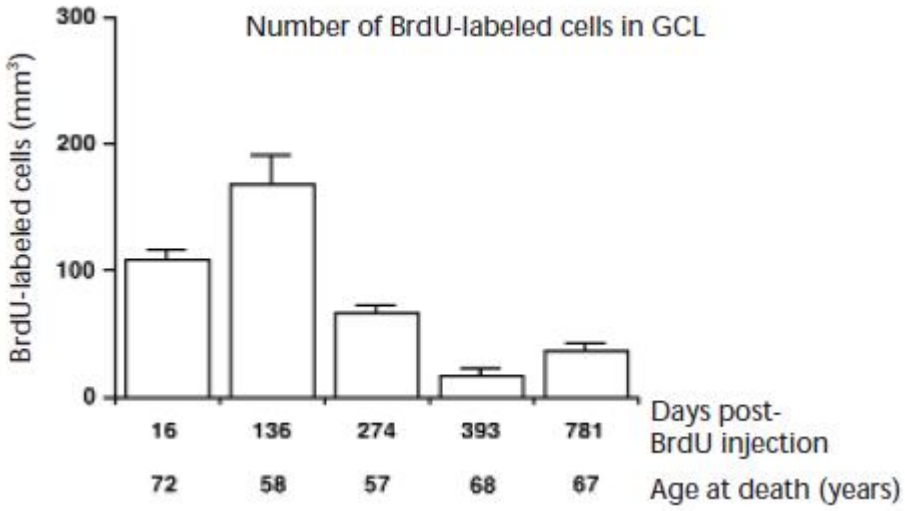
- New neurons are generated in the adult human hippocampus.

  BrdU labels cells in SGZ and granule cell layer.

  More labeled cells in SGZ with shorter post injection survival, and more cells in granule layer with longer post injection survival.

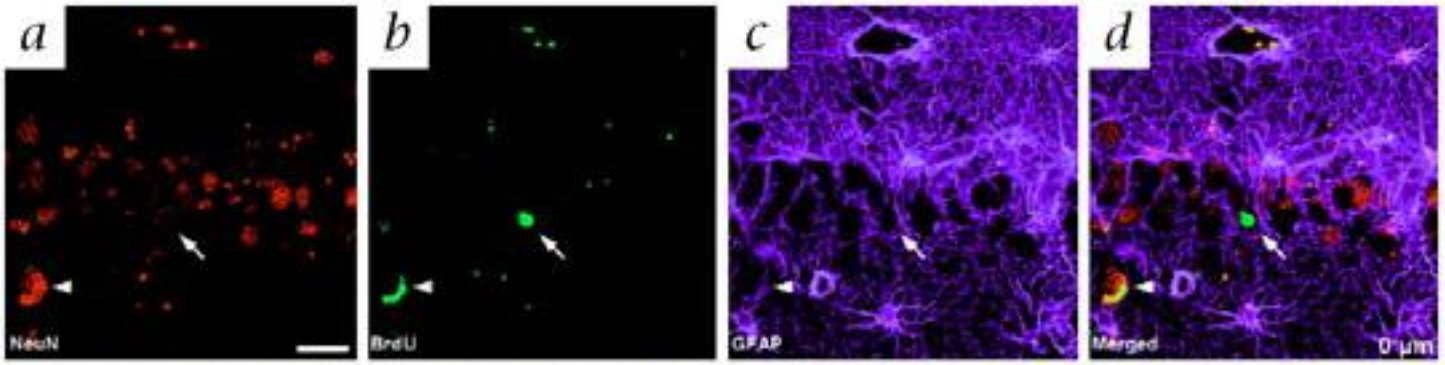






Subgranule Zone (SGZ)

BrdU+ cells express neuronal or glial markers.



Subgranule Zone (SGZ)

- New neurons have a role in learning and memory.

  Reduced neurogenesis with an antimitotic agent or with irradiation reduced learning in several paradigms.

  Spatial learning tasks were enhanced with treatments that increased neurogenesis.

Subgranule Zone (SGZ)

- Neurogenesis also appears to result in forgetting previous hippocampal dependent learning (Akers KG et al., 2014).

  Young animals with rapid hippocampal neurogenesis are more likely to forget spatial learning than old animals with little neurogenesis.

  Experimentally increasing or decreasing SGZ neurogenesis resulted in proportional forgetting.

[Maybe we have a finite ability to learn spatial concepts, and new learning requires loss of old learning.]

Subgranule Zone (SGZ)

- Factors that regulate SGZ neurogenesis:
- Stress reduces neurogenesis, as do glucocorticoids; stress increases glucocorticoid release by the adrenal gland (adrenal cortex).
- Sleep deprivation reduces neurogenesis.
- An enriched environment increases neurogenesis.
- Exercise increases neurogenesis.
- Sex increases neurogenesis.
- Antidepressants increase neurogenesis.
- Ethanol reduces neurogenesis.

Subgranule Zone (SGZ)

- BMP inhibits neurogenesis.
- Sleep or exercise decreases the level of BMP in the SGZ.

(Kessler J seminar, 2014)

Subgranule Zone (SGZ)

Fluoxetine, a commonly used antidepressant, increased SGZ neurogenesis in rats and humans. (It is a selective serotonin reuptake inhibitor sold by the trade names Prozac and Sarafem.)

Fluoxetine ameliorated anxiety-related feeding suppression in rats.

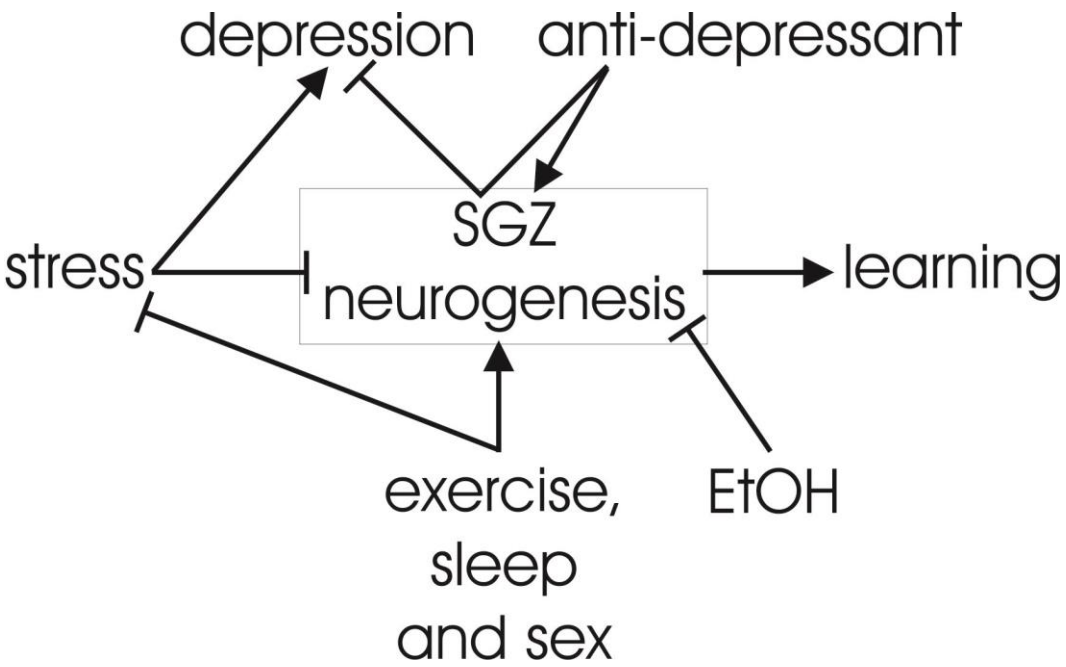
Fluoxetine had no effect on anxiety or depression if neurogenesis was blocked.

Subgranule Zone (SGZ)

- Most new neurons generated in the adult dentate gyrus die.
- Blocking cell death resulted in impaired performance in memory tasks.

(Kim WR et al. 2009)

What does this tell us?



Adult Neurogenesis (in the SVZ & SGZ)

New neurons in the adult brain undergo the same steps as neurons in the developing brain:

- Migration
- Process growth
- Synaptogenesis
- Refinement
- Cell death

New neurons start to function after about 4 weeks, and development is believed to be complete after about 2 months.

Neurogenesis in the Aged Brain

- Neurogenesis is significantly reduced in aged rats compared to young adults:

  SVZ ↓ 70%

  SGZ ↓ 80-90%

- Expression levels of numerous factors that promote neurogenesis are lower in the aged brain including BDNF, bFGF (FGF2), VEGF.

- Administration of these factors increased neurogenesis in the aged brain but did not restore it to the level seen in young adults.

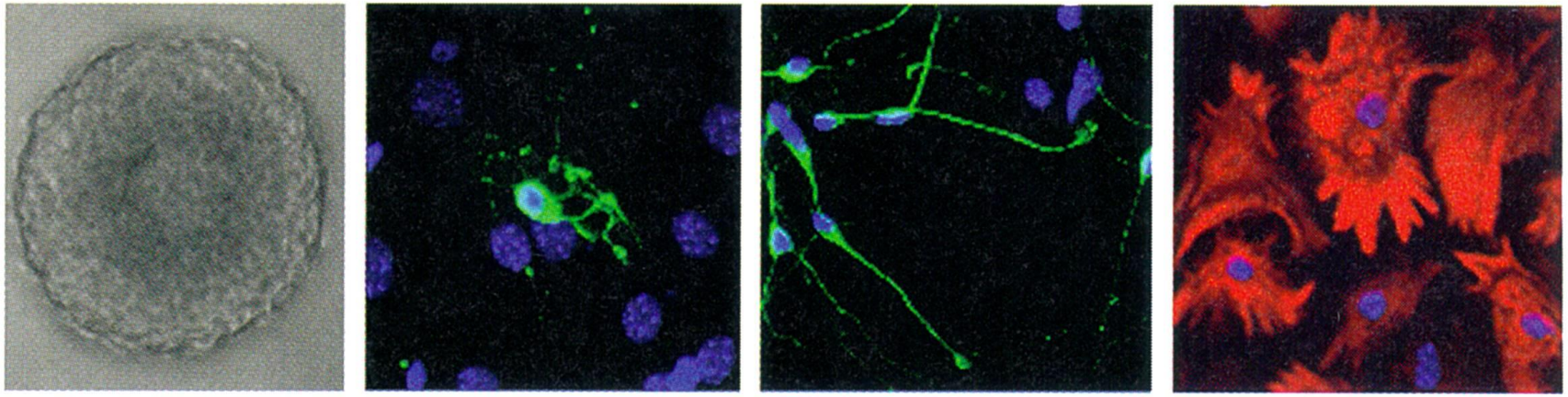
- Exercise improved neurogenesis and learning in aged rats.

Neurogenic Niche

- SVZ and SGV are special environments that promote neurogenesis.
- Progenitor cells are in close association with blood vessels.
- Niche has high levels of Wnt3, Shh, bFGF, BMPs and retinoic acid.
  - Expression of a DN-Wnt3 reduced adult neurogenesis
  - Blocking Shh signaling reduced adult neurogenesis.

Neural Stem Cells (NSCs)

- NSCs have been harvested from adult SVZ and SGZ.
- NSCs divide in vitro in the presence of EGF or bFGF (FGF2) and form ‘neurospheres’.
- Neurospheres can generate neurons, astrocytes and oligodendrocytes.



Neural Stem Cells (NSCs)

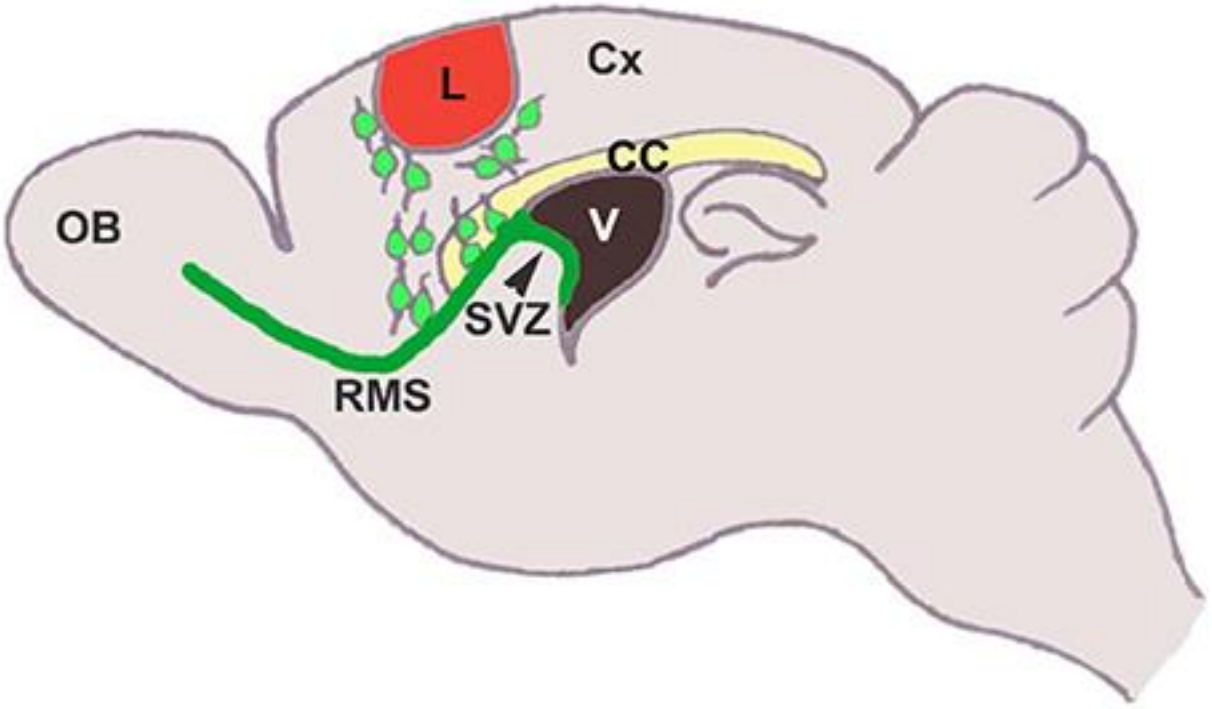
- NSCs also have been harvested from many other adult brain regions including cerebellum, midbrain and spinal cord. These cells do not generate neurons in vivo.
- NSCs from spinal cord divide and generate neurons when transplanted to SGZ but not when transplanted back to the spinal cord.

  (i.e. shows that the SGZ ‘niche’ is special)

Injury Induced Neurogenesis

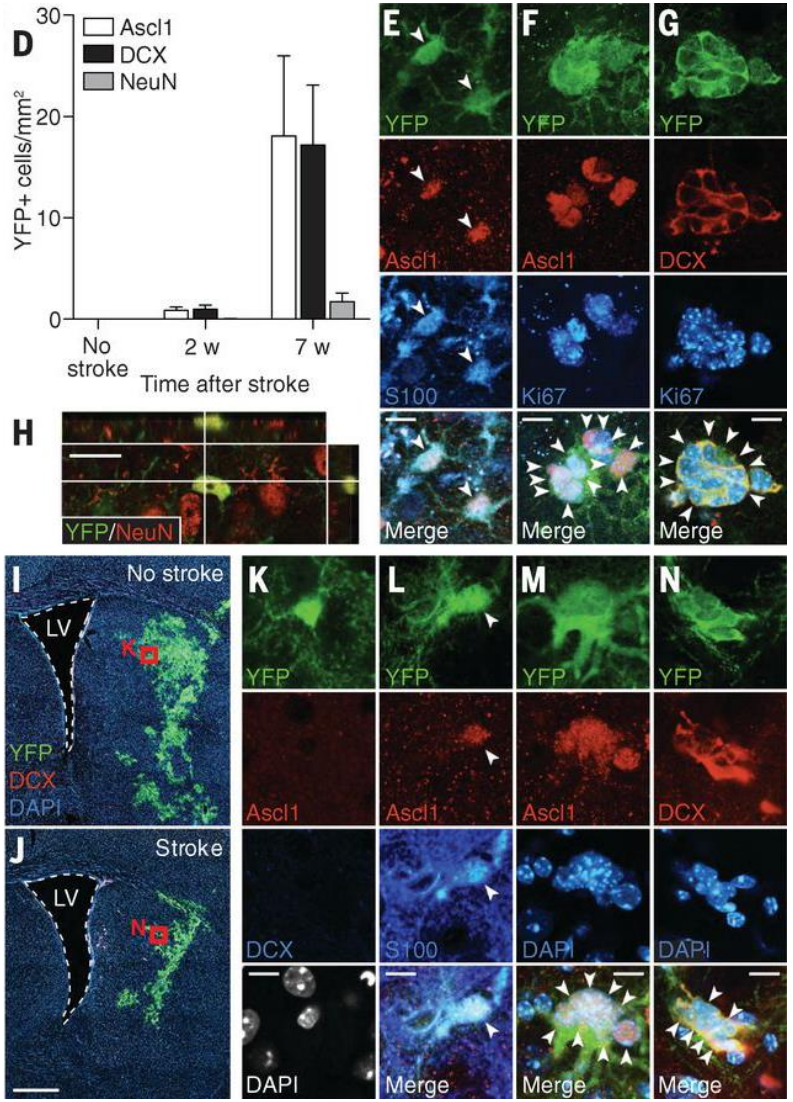
- Following injury to the cortex (e.g. stroke), some new neurons leave the RMS and migrate into the cerebral cortex.

- Injury to the brain increases neurogenesis in the SVZ and SGZ.



Injury Induced Neurogenesis

- Following a stroke, some forebrain astrocytes lose astrocyte characteristics and express neuronal characteristics.
- This response in astrocytes is initiated by a loss of Notch signaling.



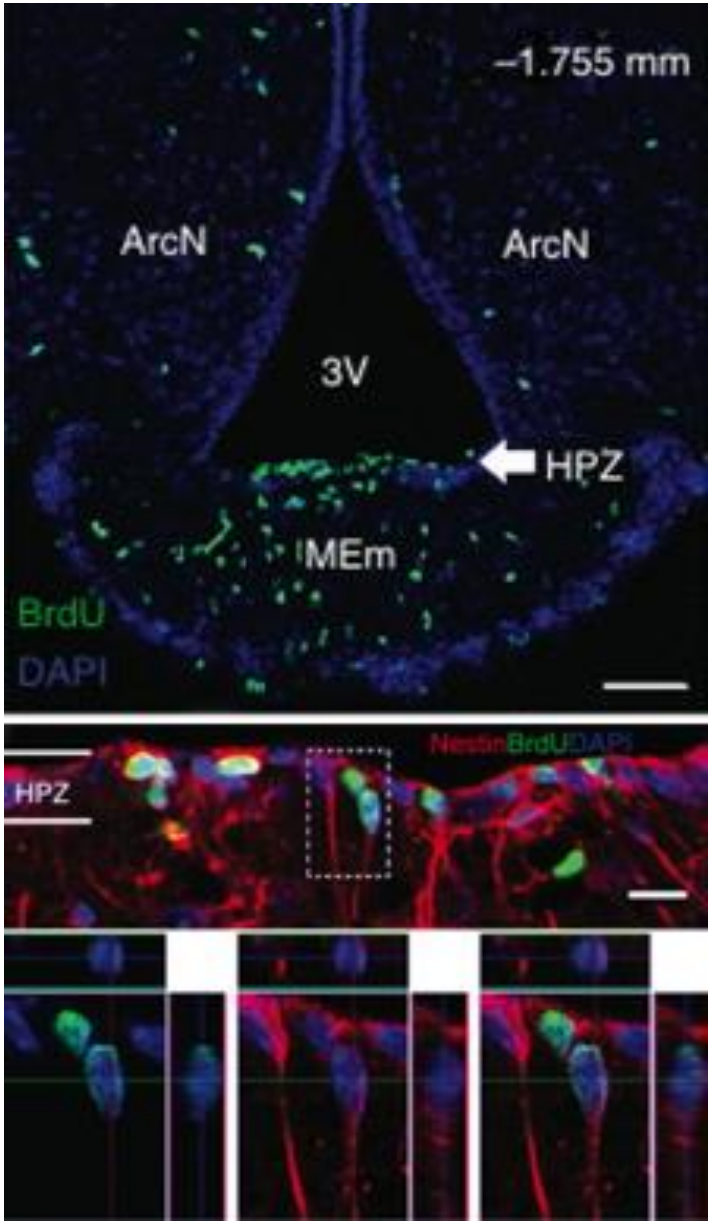
(Magnusson JP et al., 2014)

Neurogenesis in Other Regions of Adult Mammalian Brain

- Although controversial and not broadly accepted, low levels of neurogenesis have been reported in other areas of the adult mammalian brain:
  - substantia nigra (Zhao M et al., 2003)
  - amygdala & piriform cortex (Bernier PJ et al., 2002)
  - striatum & cortical interneurons (Dayer AG et al., 2005)
  - hypothalamus (Xu Y et al., 2005)

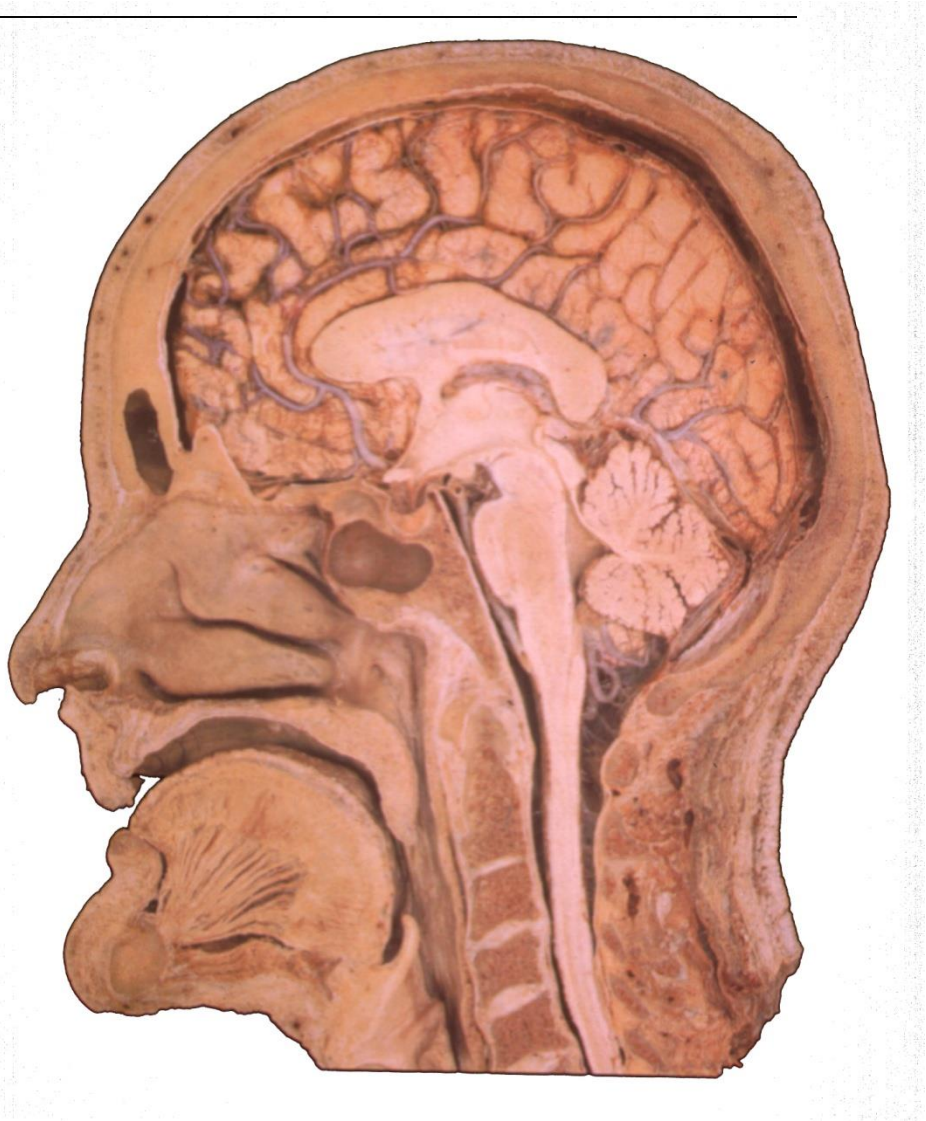
Neurogenesis in Other Regions of Adult Mammalian Brain

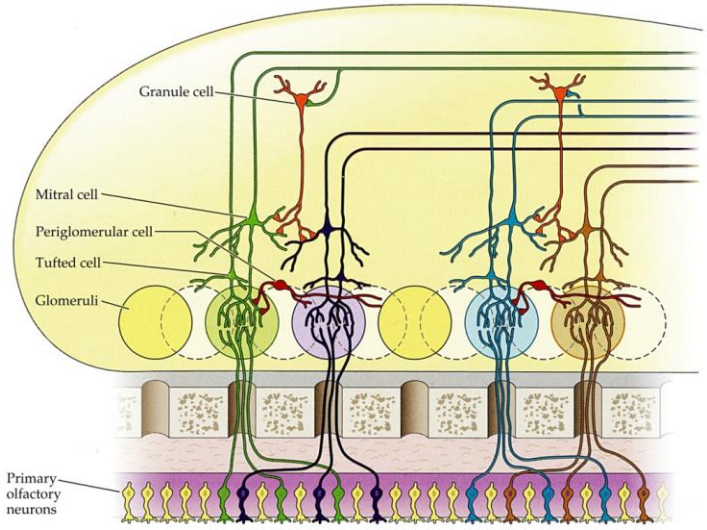
- Neurogenesis in adult hypothalamus is much less than seen in SGZ or SVZ.
- Level of neurogenesis in hypothalamus correlated inversely with weight gain in rodents.
    - Blocking neurogenesis with Ara-C treatment increased body weight.
    - Increasing neurogenesis with CNTF decreased body weight.



Neurogenesis in the Olfactory Epithelium

- New olfactory receptor neurons are continually generated in the nasal epithelium from a population of resident progenitor cells.
- The new neurons grow axons from the nose into the olfactory bulb in the brain.
- The new neurons function.
- There does not appear to be an increase in the number of receptor neurons, so neurons must continually die.



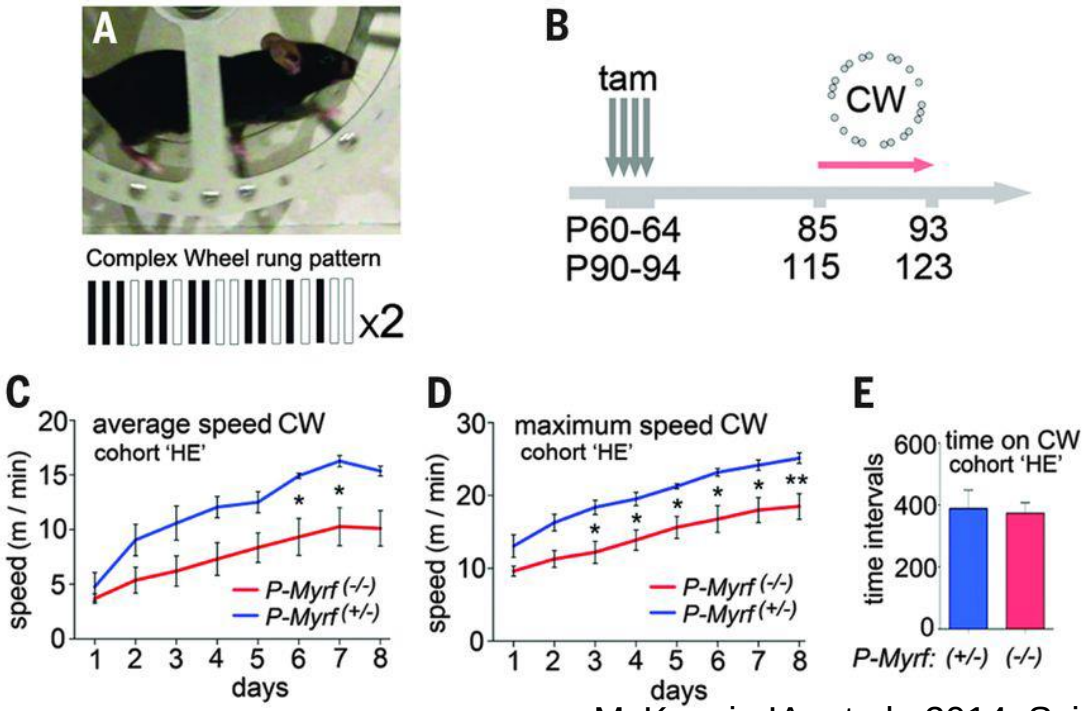


Gliogenesis in the Adult Nervous System

- Astrocytes and oligodendrocytes are produced at low levels throughout the nervous system in the adult.
- Oligodendrocytes are generated in the adult brain from oligodendrocyte precursor cells (OPCs) leading to new myelin formation.
- Demyelinating disease or injury promotes OPC division.
- In the normal brain, sleep and exercise promotes OPC division.

Gliogenesis in the Adult Nervous System

- Genesis of oligodendrocytes was prevented in adult mice with an inducible gene knockout.
- Mice not producing new oligodendrocytes were unable to learn to run on a wheel with irregularly spaced rungs.
- New oligodendrocytes are not required to recall a prelearned skill.



McKenzie IA, et al., 2014, Science 346:318

Gliogenesis in the Adult Nervous System

- Oligodendrocytes and new myelin are generated preferentially during sleep.
- Increasing or decreasing sleep resulted in a proportional change in genesis of new oligodendrocytes and myelin.

(Bellesi M, et al., 2013)