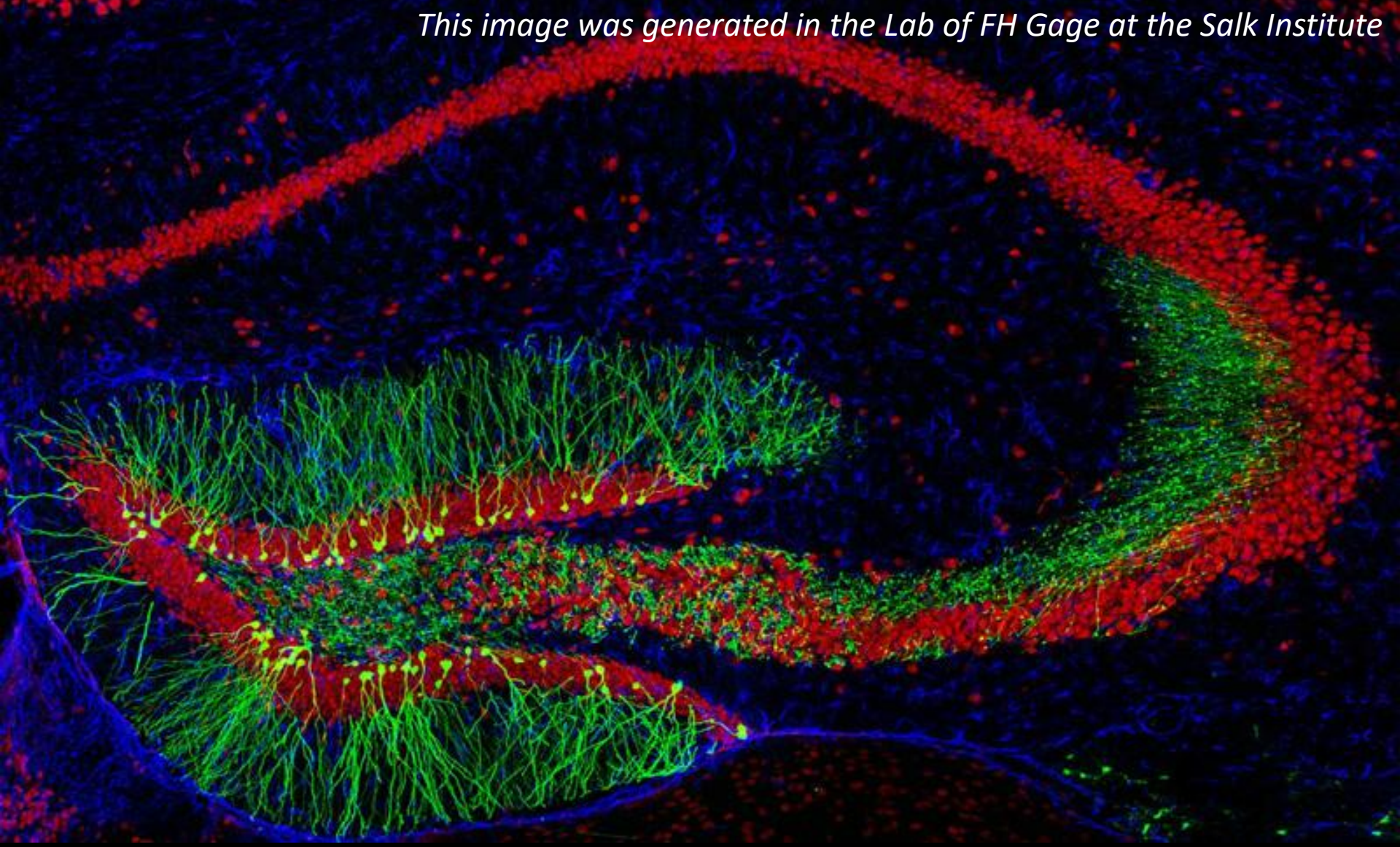


Νευρογένεση στον ενήλικο ιππόκαμπο και συμπεριφορά

Τζωρτζίνα Κουρούπη, Ελληνικό Ινστιτούτο Παστέρ

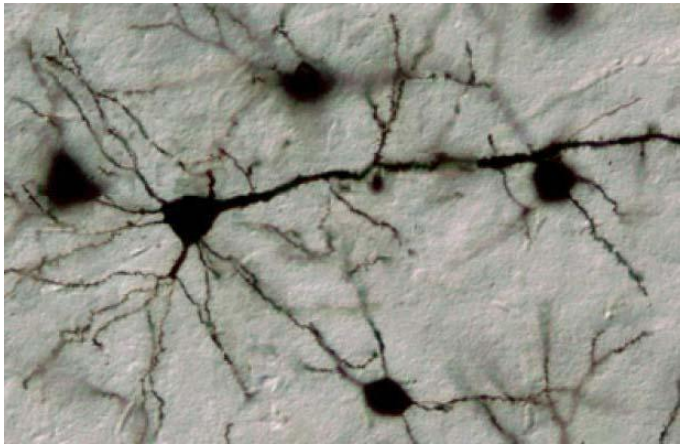
ΠΜΣ «Εφαρμοσμένη Νευροανατομία», 9 Ιουνίου 2018

Το Δόγμα

- "In the adult centers the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated." Santiago Ramon y Cajal

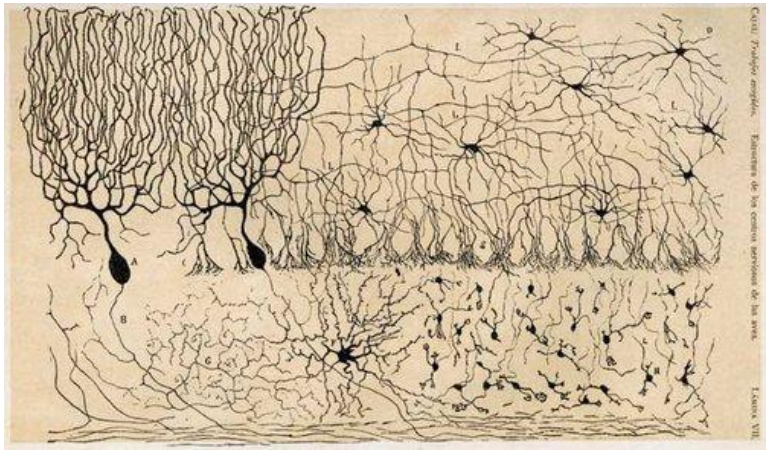
"Ο ενήλικος εγκέφαλος δεν έχει τη δυνατότητα να δημιουργεί νέους Νευρώνες"

Golgi staining



Δομή Νευρικού Κυττάρου

Drawing of Golgi-stained cerebelum by Ramón y Cajal



Ο Νευρικός Ιστός δομείται από περίπλοκα δίκτυα Νευρικών Κυττάρων

Το Δόγμα κλονίζεται!

Altman and Das, 1965

Autoradiographic and Histological Evidence of Postnatal Hippocampal Neurogenesis in Rats [1]

JOSEPH ALTMAN AND GOPAL D. DAS
Psychophysiological Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts

ABSTRACT In the autoradiograms of young rats injected with thymidine-H^3 many of the granule cells of the dentate gyrus were found labeled. The number of labeled cells declined rapidly with increased age at the time of injection. Histological studies showed the presence in young rats of a large germinal matrix of mitotic cells in the ependymal and subependymal layers of the third and lateral ventricles. The areal extent and cell population of this germinal pool declined rapidly from birth on, with a transient rise with a peak at about 15 days. During this latter period the number of "undifferentiated" cells near the granular layer of the dentate gyrus showed a rapid rise with a subsequent decline. The decline in the number of "undifferentiated" cells was accompanied by a rise in the number of differentiated granule cells. Cell counts in homologous parts of the dentate gyrus indicated a six-fold increase in the number of differentiated granule cells from birth to three months. We postulated that undifferentiated cells migrate postnatally from the forebrain ventricles to the hippocampus where they become differentiated. The possible functional significance of delayed hippocampal neurogenesis is discussed with reference to our finding of incorporation of testosterone-H^3 by cells of the hippocampus, implicating that they may function as receptors of gonadal hormones.

It is commonly held that neurons in the central nervous system of higher vertebrates are formed during embryonic development and that neurogenesis does not occur postnatally. This belief is based on the absence of neurons with mitotic figures in the brains of adult birds and mammals, in general, and the absence of signs of regenerative neuronal proliferation following brain lesions or trauma in particular. This conclusion has not been seriously questioned until recently, even though some investigators argued for the existance in the mature brain of "indifferent cells" (Schaper, 1897) or "medulloblasts" (Bailey and Cushing, '25) which can differentiate into neurons (for a history, see Globus and Kuhlenbeck, '44; Jones, '32; Kershman, '38), while others claimed to have observed mitotic neurons in young mammals (for a history, see Kjellgren, '44).

In pilot studies employing fine-resolution autoradiography, we have recently observed (Altman, '62b) that following intracranial injection of thymidine-H^3 into young adult rats there was an accumulation of reduced silver grains over the nuclei of a few neurons in the neocortex and, more commonly and consistently, over the granules cells of the hippocampus. This finding was subsequently confirmed in normal adult rats and adult cats after intraperitoneal or intraventricular injection of thymidine-H^3 (Altman, '63a). Since there is good evidence that thymidine, a specific precursor of chromosomal DNA, is utilized exclusively by the nuclei of cells that are preparing for multiplication (Hughes, '59; Hughes, et al., '58; Leblond, et al., '59; Taylor, et al., '57), these results suggested the possibility of neurogenesis in some forebrain structures in adult mammals. That the autoradiographic "labeling" of cell nuclei in the brain following injection of thymidine-H^3 is associated with cellular proliferation was supported by our observation of the labeling of a good proportion of those glia cells that were induced to multiply in regions of experimental brain lesions or in areas structurally and functionally connected with the traumatized sites (Altman, '62a). The same conclusion could also be drawn from the finding that neuroglia and microglia cells

[1] This study was supported by the U. S. Atomic Energy Commission, and supplementary aid was received from the John A. Hartford Foundation. We wish to thank Elizabeth Altman, William J. Anderson and Louise Wasserman for their assistance in various phases of this program.

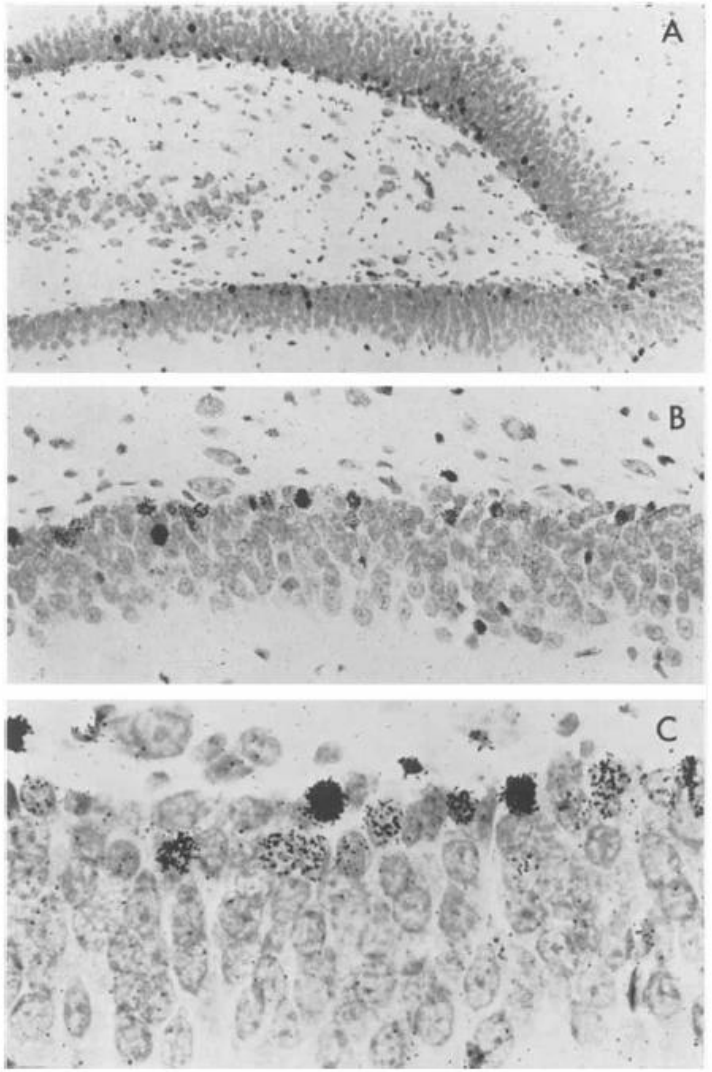


Fig. 1 Low and high power microphotographs of autoradiograms from the area of the dentate gyrus of the hippocampus in a rat injected with thymidine-H^3 at the age of ten days and killed two months after the injection. Note labeling of granule cells, predominantly in the internal border (basal surface) of the granular layer. A, 100 ×; B, 256 ×; C, 640 ×.

Το Δόγμα καταρρέει εντελώς!

20 years ago…
Eriksson et al., Nature 1998

1998 Nature America Inc. • http://medicine.nature.com

Neurogenesis in the adult human hippocampus

PETER S. ERIKSSON[1,4], EKATERINA PERFILIEVA[1], THOMAS BJÖRK-ERIKSSON[2], ANN-MARIE ALBORN[1], CLAES NORDBORG[3], DANIEL A. PETERSON[4] & FRED H. GAGE[4]

Department of Clinical Neuroscience, Institute of Neurology[1], Department of Oncology[2], Department of Pathology[3], Sahlgrenska University Hospital, 41345 Göteborg, Sweden
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The genesis of new cells, including neurons, in the adult human brain has not yet been demonstrated. This study was undertaken to investigate whether neurogenesis occurs in the adult human brain, in regions previously identified as neurogenic in adult rodents and monkeys. Human brain tissue was obtained postmortem from patients who had been treated with the thymidine analog, bromodeoxyuridine (BrdU), that labels DNA during the S phase. Using immunofluorescent labeling for BrdU and for one of the neuronal markers, NeuN, calbindin or neuron specific enolase (NSE), we demonstrate that new neurons, as defined by these markers, are generated from dividing progenitor cells in the dentate gyrus of adult humans. Our results further indicate that the human hippocampus retains its ability to generate neurons throughout life.

Loss of neurons is thought to be irreversible in the adult human brain, because dying neurons cannot be replaced. This inability to generate replacement cells is thought to be an important cause of neurological disease and impairment. In most brain regions, the generation of neurons is generally confined to a discrete developmental period. Exceptions are found in the dentate gyrus and the subventricular zone of several species that have been shown to generate new neurons well into the postnatal and adult period[1–6]. Granule neurons are generated throughout life from a population of continuously dividing progenitor cells residing in the subgranular zone of the dentate gyrus in the rodent brain[3]. 'Newborn' neurons generated from these progenitor cells migrate into the granule cell layer, differentiate, extend axons and express neuronal marker proteins[7–10].

We examined whether progenitor cells reside in the adult human hippocampus and whether new neurons are born within the dentate gyrus of the adult human brain. Postmortem tissue from the hippocampus and the subventricular zone of caudate nucleus was obtained from cancer patients ($n = 5$) who received one intravenous infusion (250 mg; 2.5 mg/ml, 100 ml) of bromodeoxyuridine (BrdU) for diagnostic purposes[11]. One patient diagnosed with a similar type and location of cancer, but without BrdU treatment, was included as a control. A thymidine analog, BrdU is incorporated into the DNA of dividing cells and can be detected immunohistochemically in their progeny[5,12,13].

Cell genesis and survival in the adult human dentate gyrus
The number of surviving labeled, proliferating progenitors was

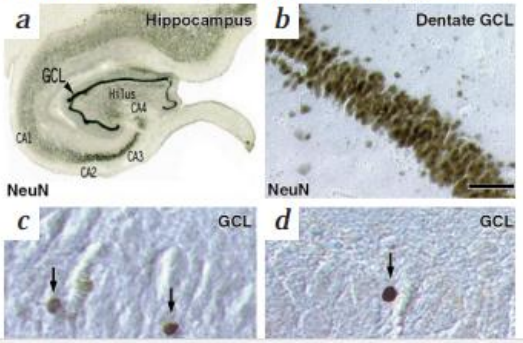
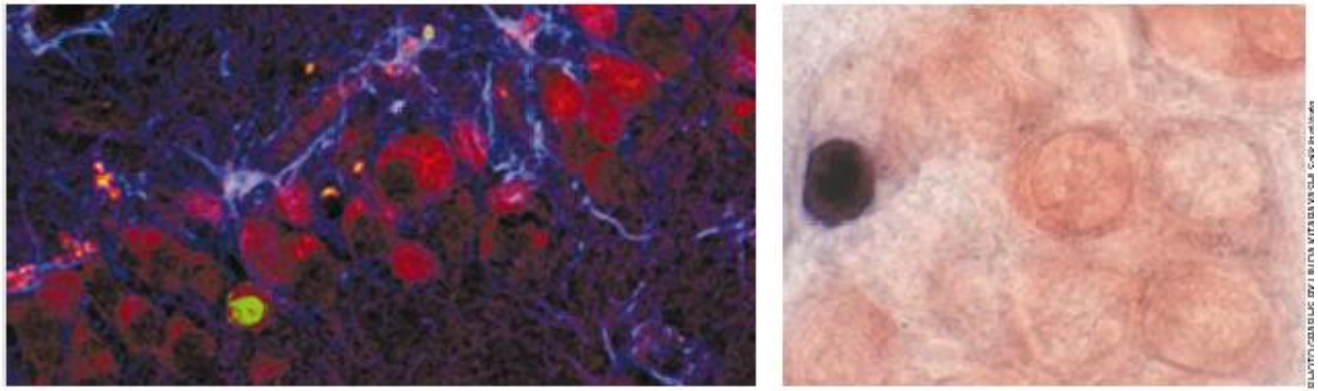


Fig. 1 Newly generated cells can be detected in the adult human brain in patients previously treated with BrdU. *a*, The hippocampal region of the adult human brain immunoperoxidase-stained for the neuronal marker NeuN. *b*, The hippocampal dentate gyrus granule cell layer (GCL) visualized

Το Δόγμα καταρρέει εντελώς!

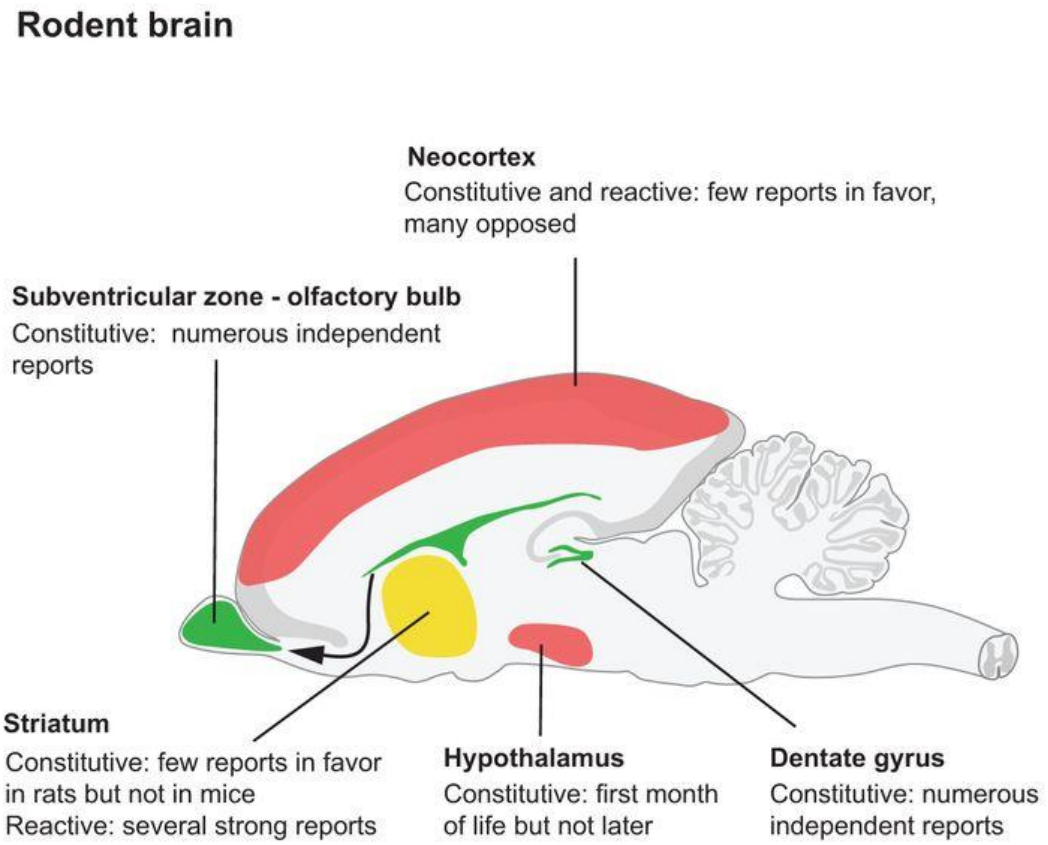
20 years ago…
Eriksson et al., Nature 1998

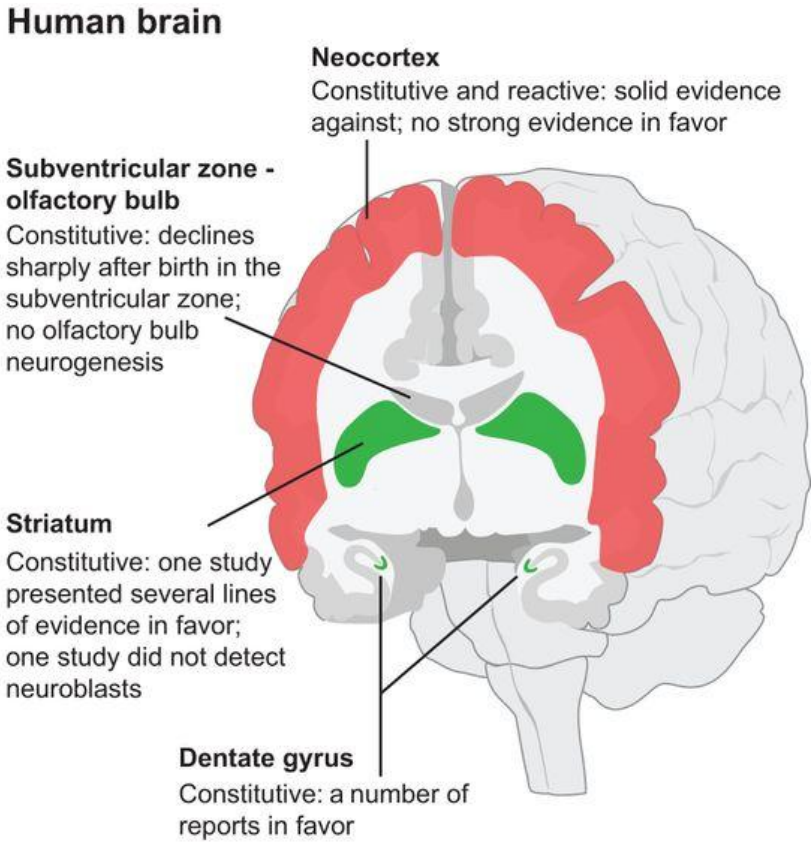


PROOF OF NEURON FORMATION in the mature human brain includes these micrographs of hippocampal tissue from adults who died of cancer. The images, derived through different methods, mark neurons in red. The green in a neuron in the left image and the dark shading of a neuron in the right image reveal that the cells' chromosomes harbor a substance—bromodeoxyuridine (BrdU)—that was injected into the patients to assess tumor growth. BrdU becomes integrated into the DNA of dividing cells (such as stem cells) but is not retained by already established neurons. Its presence therefore signals that the marked cells differentiated into neurons only after the BrdU was delivered, late in the patients' lives.

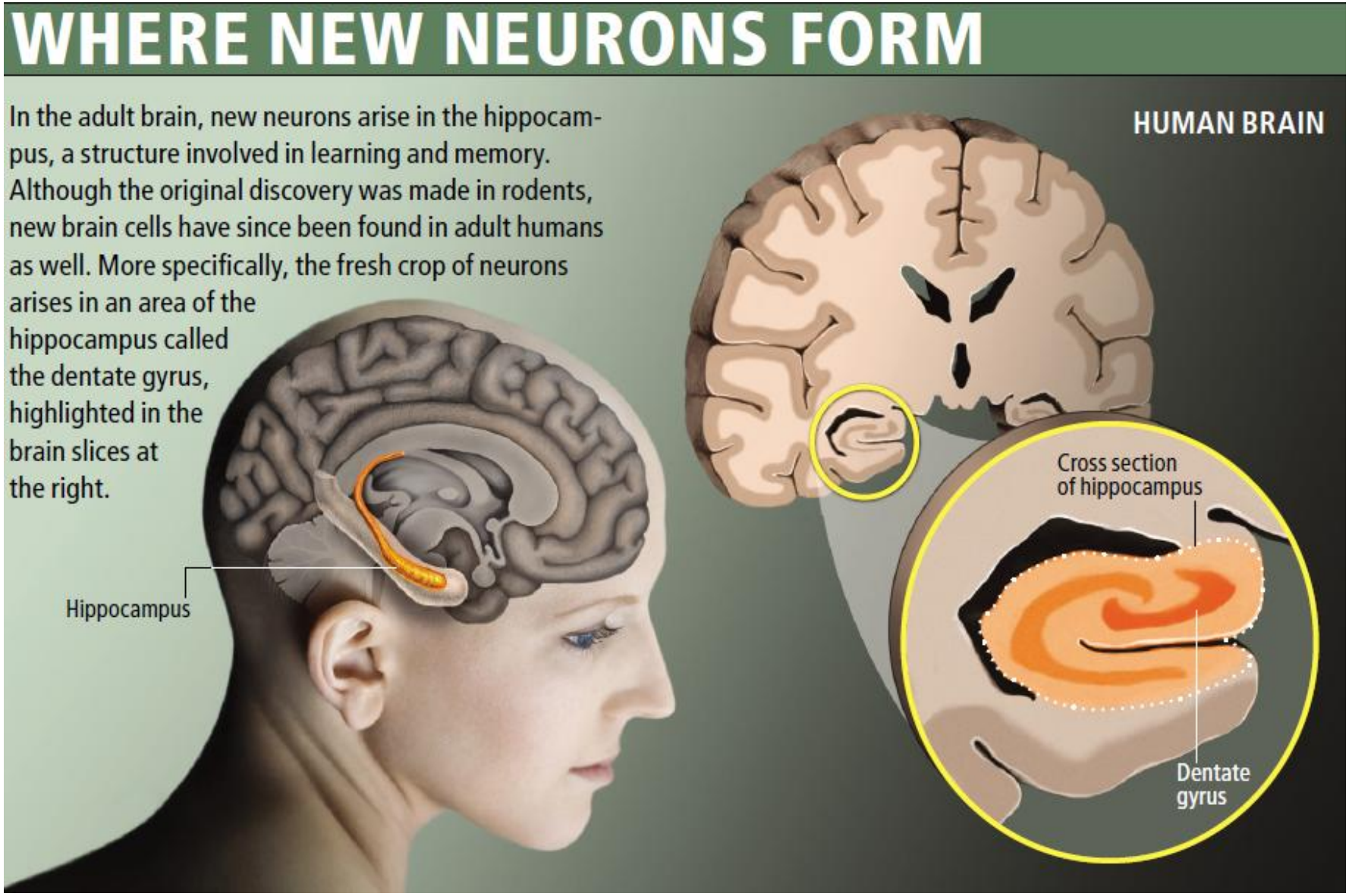
- The study provided strong evidence for the presence of adult neurogenesis in humans
- It did not enable any quantitative estimates
- … whether adult neurogenesis decreased with primate evolution, and whether the extent of this process in humans is sufficient to have any functional impact

The extent of neurogenesis in different regions of the adult brain

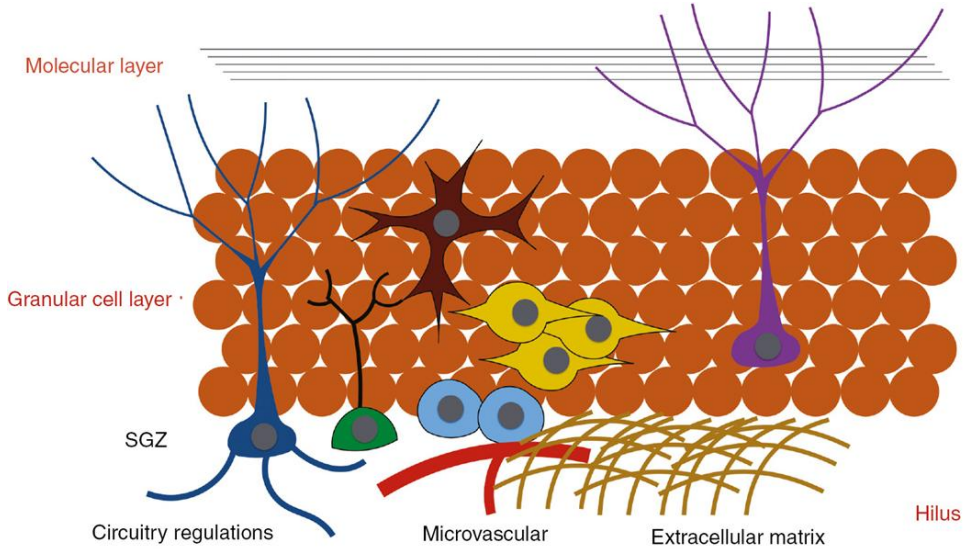


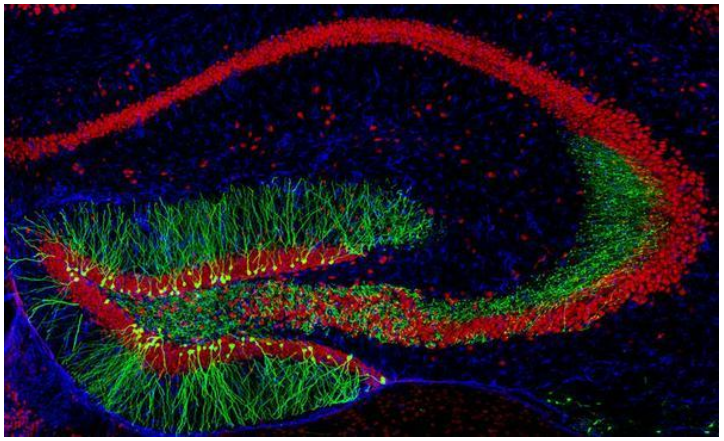


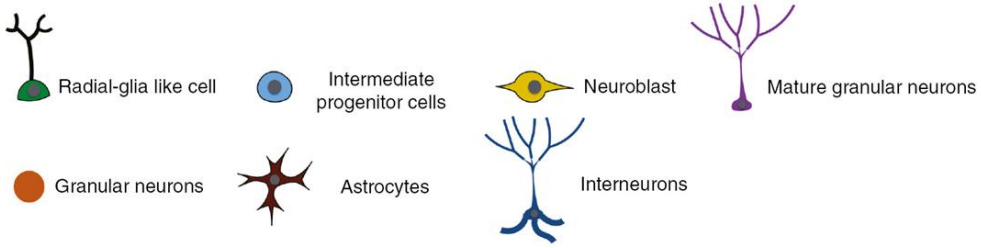
Adult neurogenesis in the subgranular zone of the dentate gyrus in the hippocampus
Νευρογένεση στην υποκοκκιώδη ζώνη της οδοντωτής έλικας του ιπποκάμπου

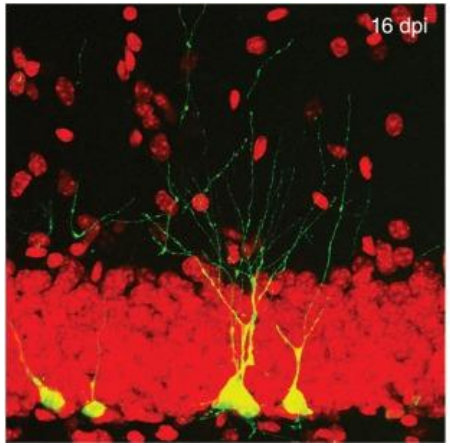


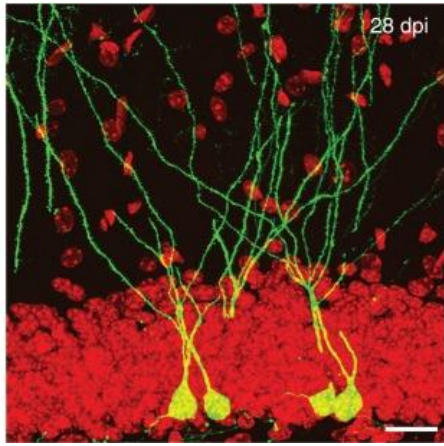
Adult neurogenesis in the SGZ



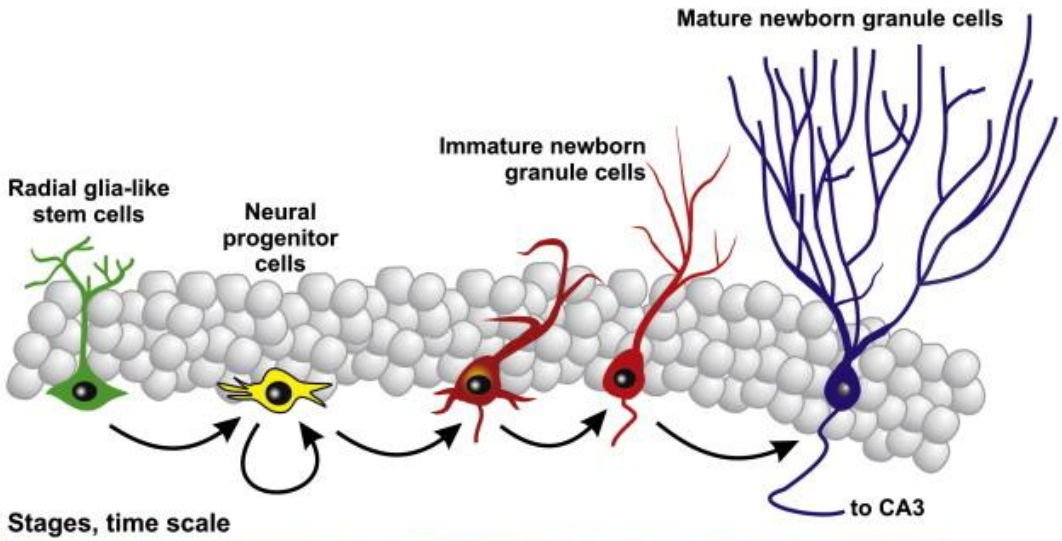








Adult Neural Stem Cells – Hippocampus (DG)



Stages, time scale

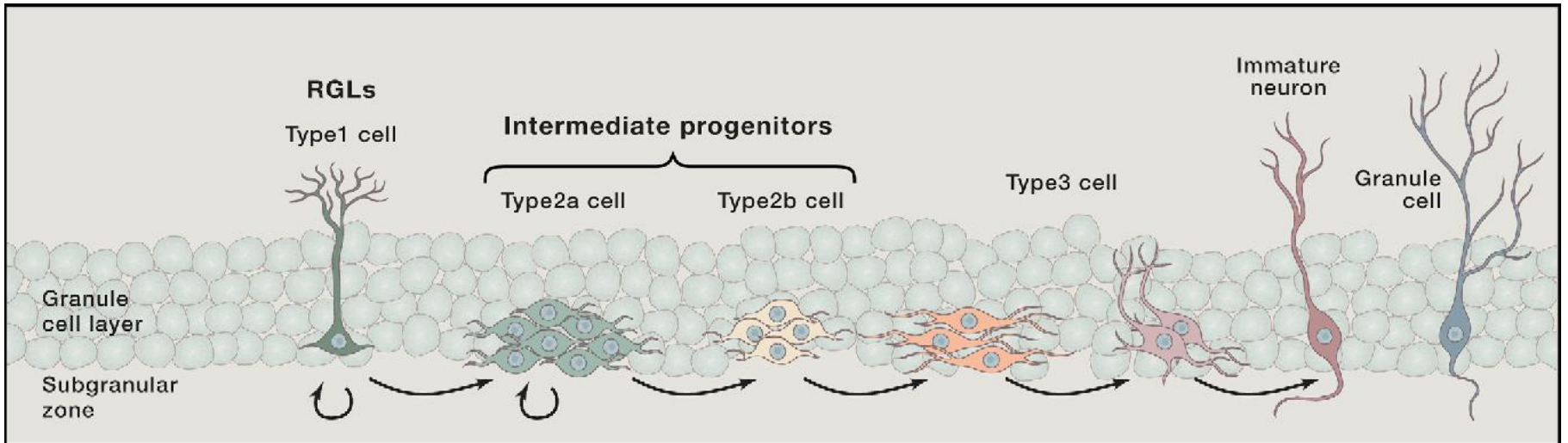
Proliferation	Fate specification	Differentiation Migration	Synaptic integration
~ 25 h	~ 4 days	~ 4-10 days	~ 2-4 weeks

Marker expression

GFAP, Nestin, Sox2	DCX, PSA-NCAM, TuJ1	NeuN, Calbindin

Expansion phase		Survival and elimination phase	
Radial glia-like stem cells	Transiently amplifying progenitor cells	Dendrite extension Axon extension Increased synaptic plasticity Activity dependent recruitment Survival or apoptosis	Maturation of dendritic spines Lowered treshold for LTP Increased synaptic plasticity

Signals, Transcription Factors, and Epigenetic Regulators during Adult Hippocampal Neurogenesis



	Quiescence	Proliferation/ Activation	Fate specification	Morphogenesis and differentiation	Maturation
Signals	BMP, Notch, GABA	Canonical Wnt, IGF, Shh, FGF-2, EGF, Dopamine	Canonical Wnt, NT-3	Wnt/PCP, Notch, BDNF, Reelin, GABA	Glutamate, NRG2, Neuronal activity
Transcription factors	Hes5, FoxO, REST	Sox2, Tlx	Tbr2, Ascl1/Mash1, NeuroD1, Prox1	NeuroD1,Prox1, CREB, AP-1?	CREB
Epigenetic regulation		Gadd45b, LSD1	Fmrp, Mbd1	Gadd45b, MeCP2	MeCP2, HDAC2

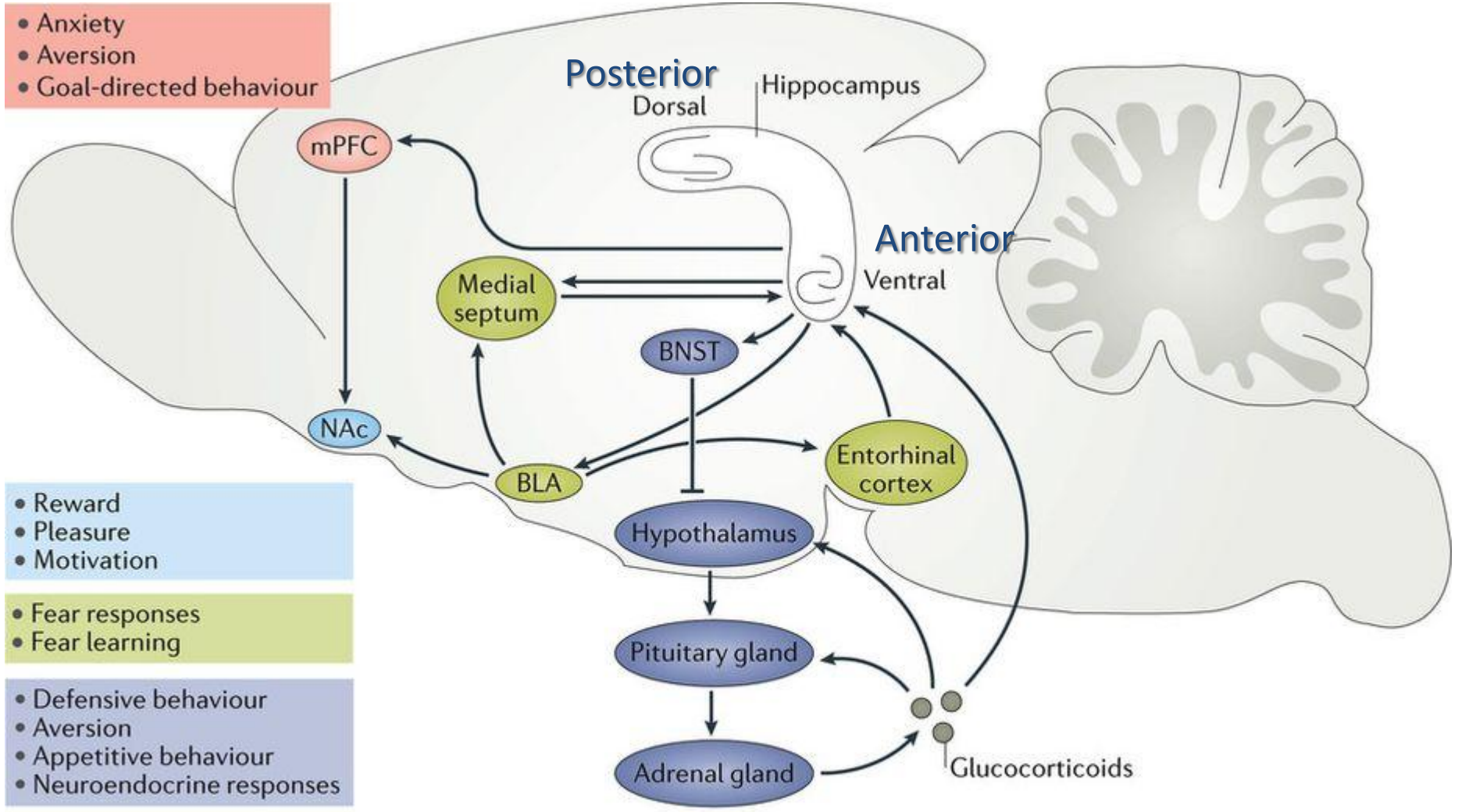
Goncalves et al., *Cell 2016*

Adult hippocampal neurogenesis and cognitive flexibility — linking memory and mood

Cognitive flexibility: A cognitive process of executive function by which previously learned behavioral strategies can be modified to adapt to changes in environmental contingencies.
Enables adaptation to new situations by switching from previously held beliefs or thoughts to new response strategies.

Anacker & Hen, Nat Rev Neurosci 2017

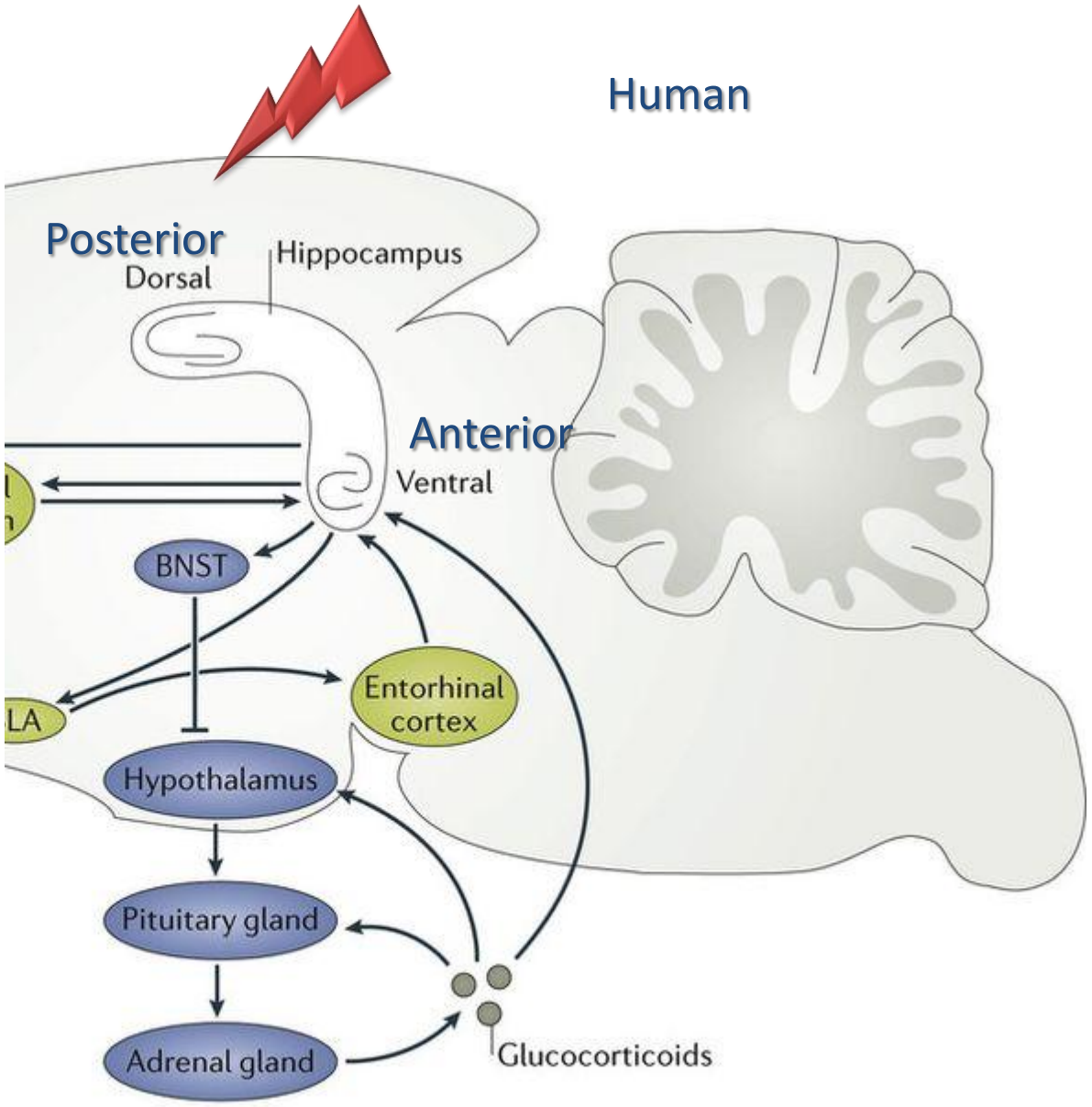
The hippocampus is a **heterogeneous structure** with gradually segregated functional differences along its dorso-ventral axis



Nature Reviews | Neuroscience

- Lesions of the **dorsal** hippocampus primarily impair **cognition** and **spatial learning**

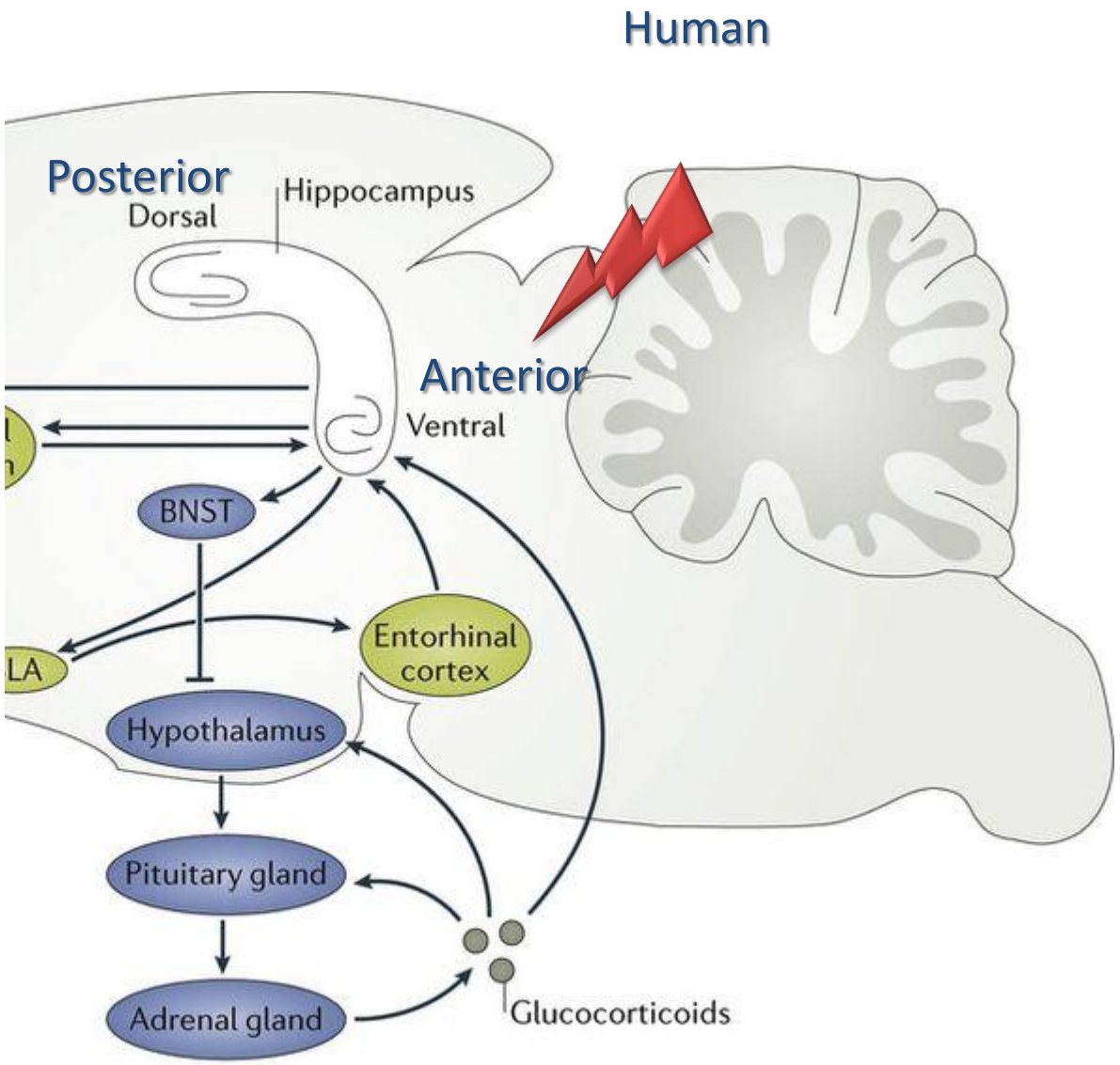
- In humans, the **posterior** hippocampus, which is analogous to the **dorsal** hippocampus in rodents, is **larger** in individuals who require a large capacity for processing spatial and contextual information, such as **taxi drivers**.



Nature Reviews | Neuroscience

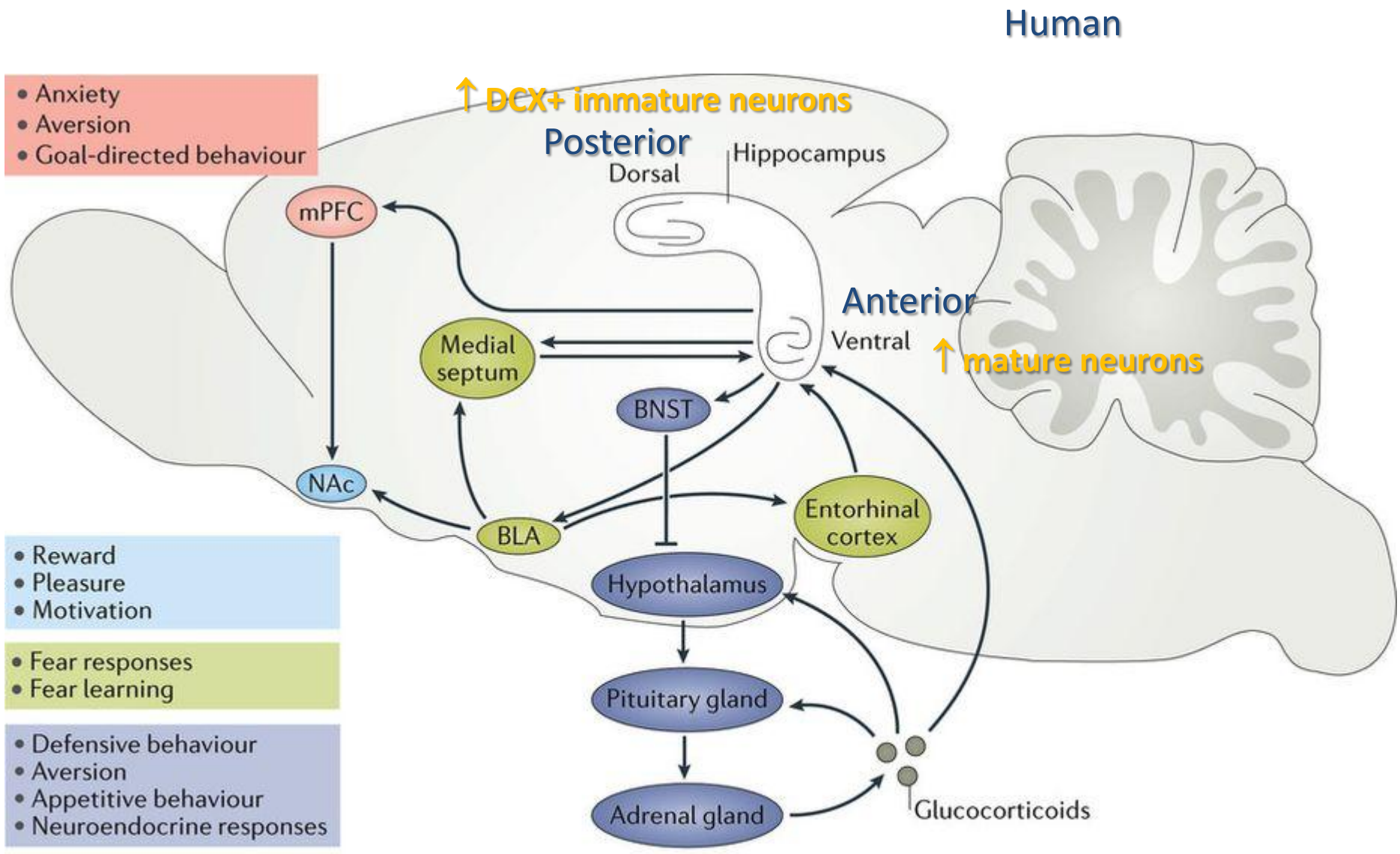
- Lesions of the **ventral** hippocampus alter **emotional behavior**, social interactions and **stress resilience**

- In humans, the **anterior** hippocampus, which is analogous to the **ventral** hippocampus in rodents, is **smaller** in unmedicated patients with **depression** and larger in antidepressant-treated patients than in healthy individuals



Nature Reviews | Neuroscience

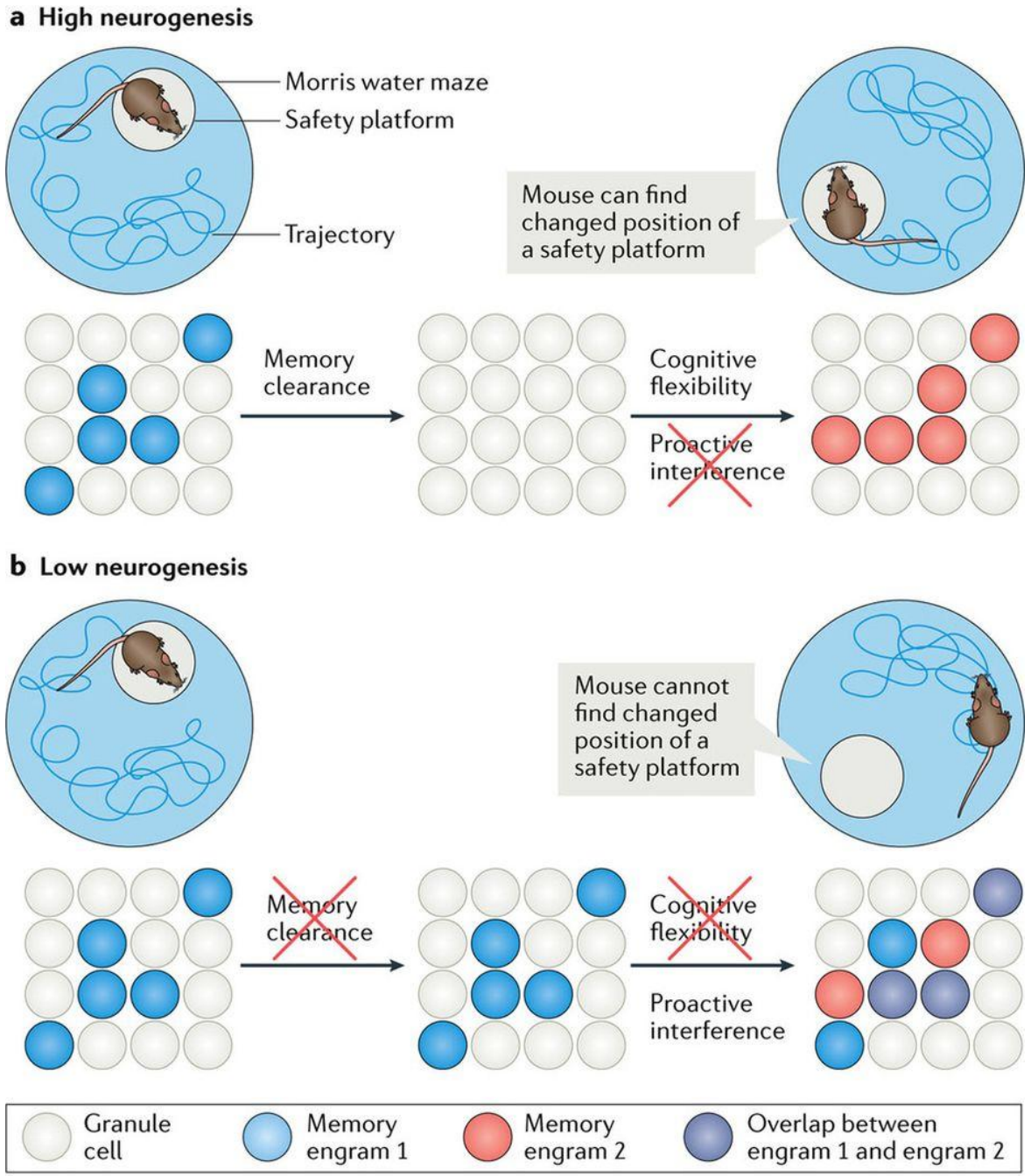
The ventral hippocampus and the neural circuitry of mood and anxiety



Nature Reviews | Neuroscience

Neurogenesis facilitates cognitive flexibility by allowing the formation of new distinct memory traces

Hippocampal neurogenesis may be necessary for cognitive flexibility, as it allows the avoidance of interference between novel and previously formed memories



MEMORY TRACES

Nature Reviews | Neuroscience

To sum up…

- The **hippocampus** has repeatedly been implicated in **learning and memory**, as well as in the **behavioral response to stress** and in the pathophysiology of **mood disorders**.
- Adult neurogenesis in the DG has been proposed to regulate **information processing** in the hippocampus, and young neurons may contribute to the circuitry both by integrating new information and by inhibiting the activity of the dense network of mature granule cells.
- This inhibitory effect of adult-born neurons may be important to **erase previously established**, fear-associated memories and to allow new, non-fear-associated memories to be formed instead (**cognitive flexibility**).
- At the same time, inhibition may facilitate sparse encoding of new information (**pattern separation**).
- **Increasing neurogenesis** or enhancing cognitive flexibility may thus represent promising new treatment strategies for patients with compromised DG gyrus function, **facilitating efficient stress recovery** and **preventing or counteracting the development of chronic psychopathology.**

March 2018

Questioning human neurogenesis

Neurons are born in the brain's hippocampus throughout adulthood in mammals, contributing to the region's functions in memory and mood. **But a study now questions whether this phenomenon really extends to humans.**

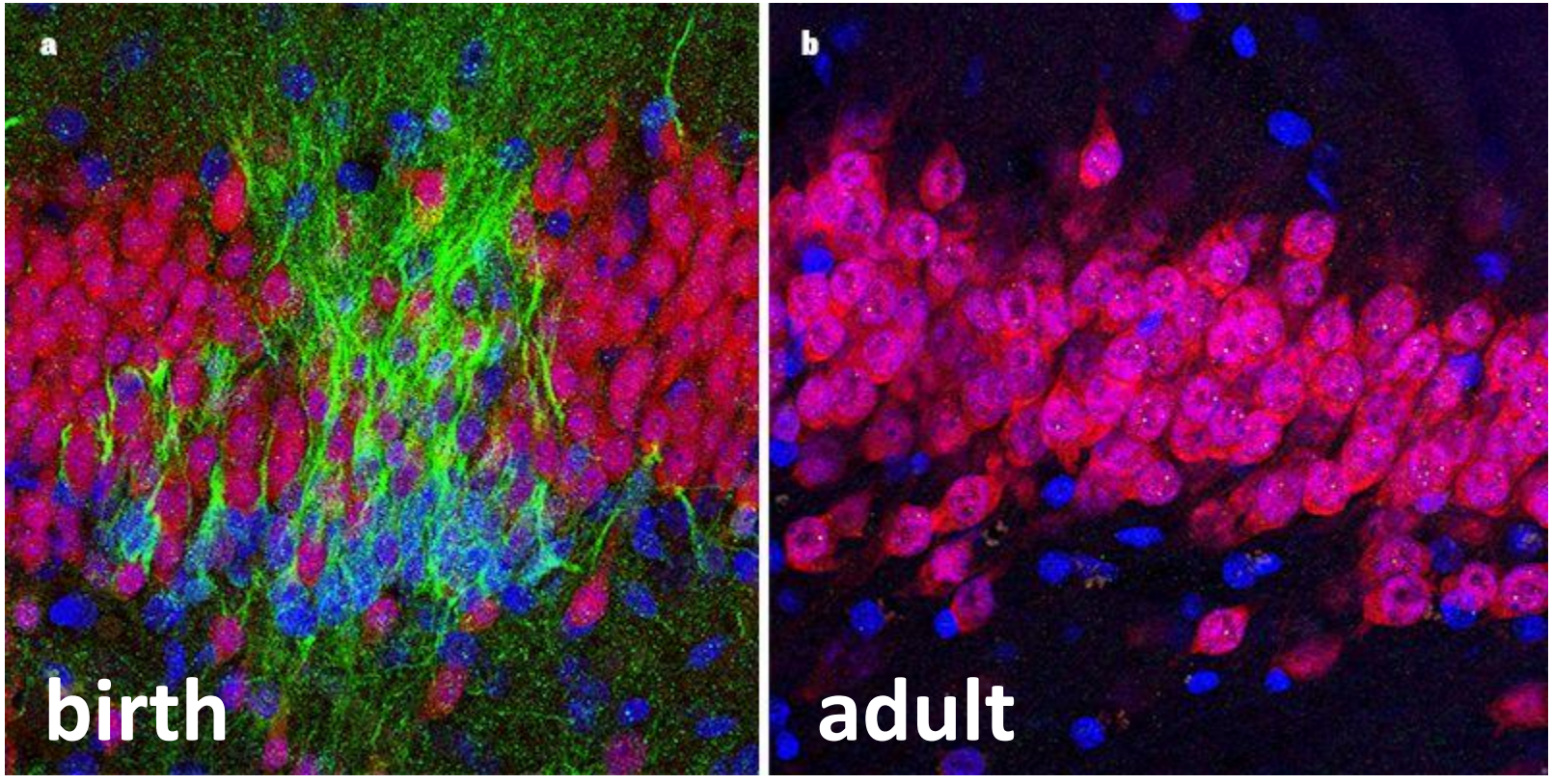
LETTER

doi:10.1038/nature25975

Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults

Shawn F. Sorrells[1,2*], Mercedes F. Paredes[1,3*], Arantxa Cebrian-Silla[4], Kadellyn Sandoval[1,3], Dashi Qi[5], Kevin W. Kelley[1], David James[1], Simone Mayer[1,3], Julia Chang[6], Kurtis I. Auguste[2], Edward F. Chang[2], Antonio J. Gutierrez[7], Arnold R. Kriegstein[1,3], Gary W. Mathern[8,9], Michael C. Oldham[1,2], Eric J. Huang[10], Jose Manuel Garcia-Verdugo[4], Zhengang Yang[5] & Arturo Alvarez-Buylla[1,2]

DCX NeuN DAPI



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Human tissue collection

37 post-mortem specimens from controls

22 post-operative neurosurgical specimens from patients with epilepsy

18–77 years of age

For infant cases, when the brain was at full term (37–40 gestational weeks) and autopsy was performed within two days after birth, we refer to the case as '**birth**'

Human DG proliferation declines sharply during infancy and a layer of proliferating progenitors does not form in the SGZ

The number of Ki-67+Sox1+ or Ki-67+Sox2+ cells decreased in the hilus during the first year of life, but these cells did not form a discrete layer beneath the GCL at any of the ages studied.

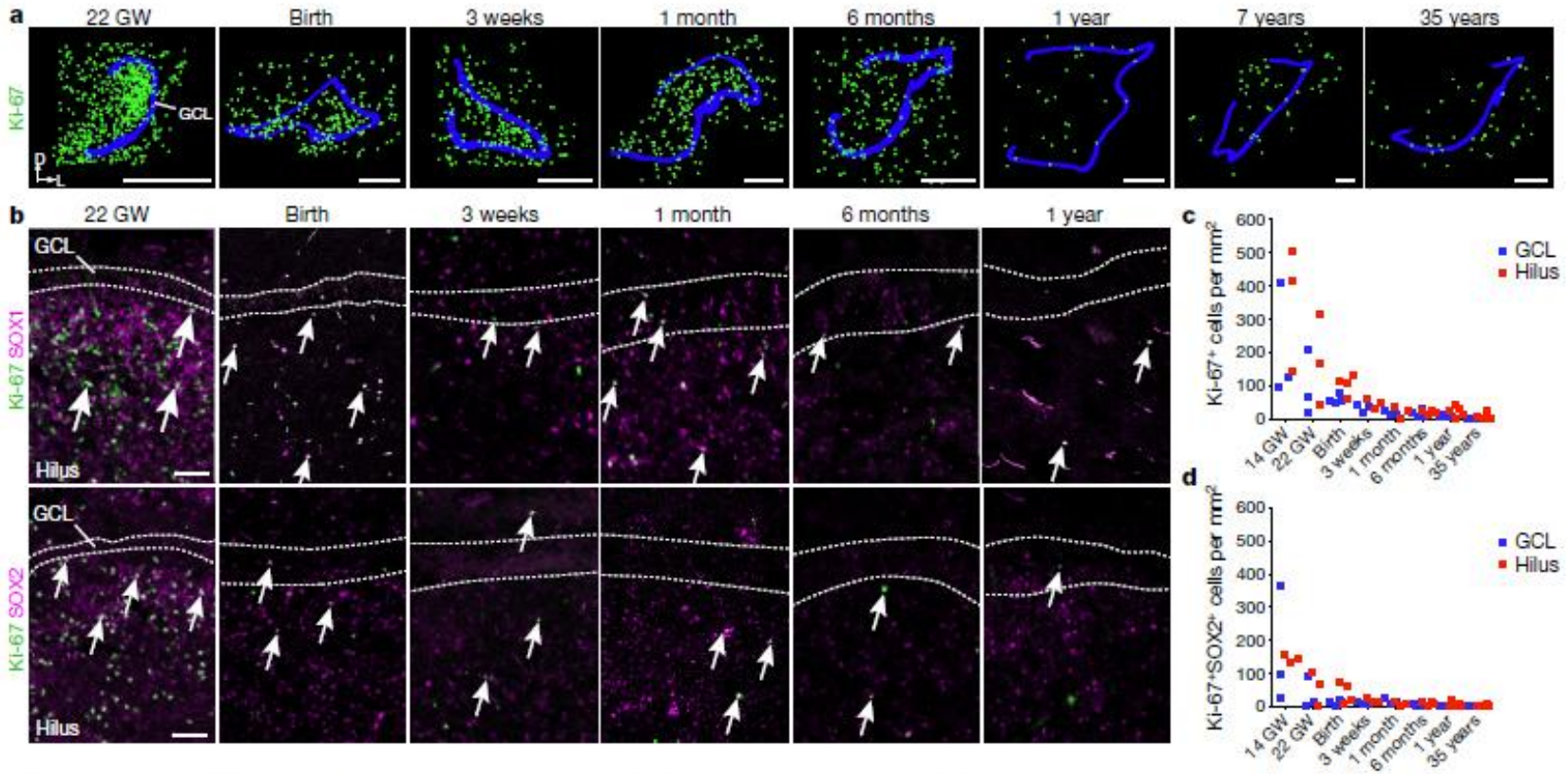


Figure 2 | Human DG proliferation declines sharply during infancy and a layer of proliferating progenitors does not form in the SGZ. **a**, Maps of Ki-67$^+$ (green) cells in the DG from samples of individuals that were between 22 gestational weeks and 35 years of age; GCL in blue. **b**, Ki-67$^+$SOX1$^+$ and Ki-67$^+$SOX2$^+$ cells (arrows) are distributed across the hilus and GCL and the number of double-positive cells decreases between 22 gestational weeks and 1 year of age. **c**, **d**, Quantification of Ki-67$^+$ (**c**) and Ki-67$^+$SOX2$^+$ (**d**) cells in the hilus and GCL. For quantifications, dots indicate staining replicates ($\geq$3) (each age $n = 1$). Scale bars, 1 mm (**a**) and 100 μm (**b**).

The number of young neurons declines in the human DG from infancy into childhood

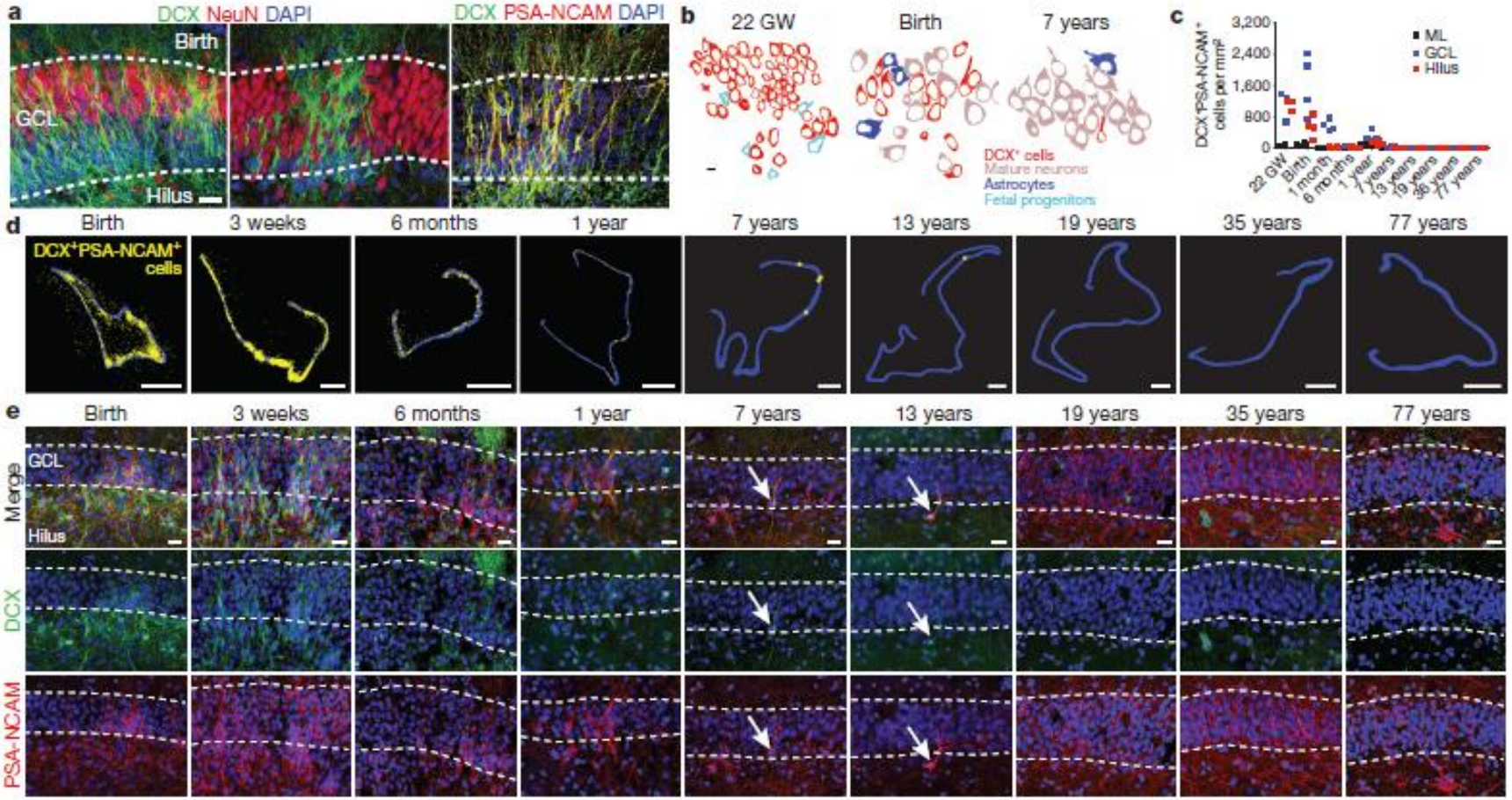


Figure 3 | The number of young neurons declines in the human DG from infancy into childhood. a, DCX^+ cells at birth are distributed in a continuous field (left) or tight clusters (middle) and express PSA-NCAM (right). **b**, Outlines of cell types in the GCL at 22 gestational weeks, birth and 7 years of age. **c**, Quantification of $DCX^+PSA\text{-}NCAM^+$ cells in the DG. **d**, Maps of $DCX^+PSA\text{-}NCAM^+$ cells (yellow dots; GCL, blue outline). **e**, $DCX^+PSA\text{-}NCAM^+$ cells in the DG (birth to 77 years) are rare by 7 and 13 years of age (arrows). For quantifications, dots indicate staining replicates (≥ 3) (each age, $n = 1$). Scale bars, 1 mm (**d**), 20 μm (**a**, **e**) and 5 μm (**b**).

The SGZ forms during macaque development but new neurons are rare in adults

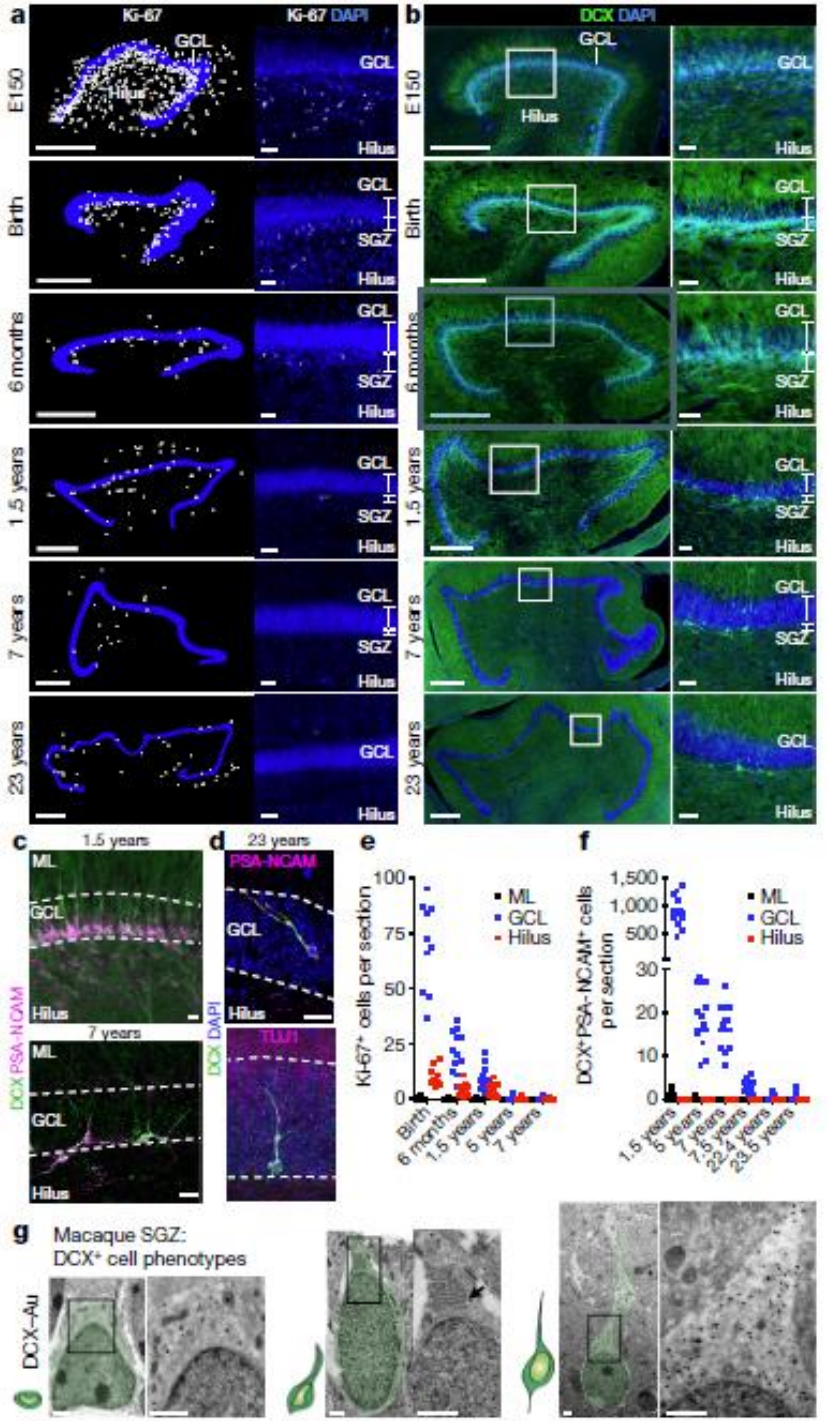


Figure 4 | The SGZ forms during macaque development but new neurons are rare in adults. **a**, **b**, Maps and immunostaining of Ki-67$^+$ cells (**a**) and DCX$^+$ cells (**b**) in the macaque SGZ (from E150 to 23 years of age). **c**, DCX$^+$PSA-NCAM$^+$ cells in the SGZ (1.5 and 7 years). **d**, DCX$^+$PSA-NCAM$^+$ or DCX$^+$TUJ1$^+$ cells (23 years). **e**, **f**, Quantification of Ki-67$^+$ cells (**e**) and DCX$^+$PSA-NCAM$^+$ cells (**f**) in the macaque GCL, hilus and molecular layer (ML). $n = 1$ animal per age; dots indicate staining replicates (≥ 3). **g**, Immunogold (DCX–Au) transmission electron microscopy of neurons (light green overlay) at different stages of maturation. Left, small DCX$^+$ cell; middle, DCX$^+$ cell with a short process, mitochondria and prominent endoplasmic reticulum (arrow); right, large DCX$^+$ cell with round soma, few organelles and an expansion into the GCL. Scale bars, 500 μm (**a**, **b** (left)), 50 μm (**a**, **b** (right)), 20 μm (**c**, **d**) and 1 μm (**g**).

To sum up…

- The authors observed the **highest number of proliferating cells and young immature neurons during the first year of life** in the dentate gyrus (DG)
- **A sharp age-dependent decrease in the number of these cells** was reported.
- Only a **few isolated young neurons** were observed by **7 and 13 years** of age.
- **No young neurons** were detected in the DG of **adult patients with epilepsy or healthy adults.**
- A similar **age-dependent reduction** was also seen in rhesus **macaques**.
- **If neurogenesis continues in the adult human hippocampus, this is a rare phenomenon**, raising questions of how human DG plasticity differs from other species in which adult hippocampal neurogenesis is abundant.
- Interestingly, a **lack of neurogenesis in the hippocampus** has been suggested for aquatic mammals (dolphins, porpoises and whales), species known for their large brains, longevity and complex behaviour.
- Understanding the limitations of adult neurogenesis in humans and other species is fundamental to interpreting findings from animal models.

One month later…

April 2018

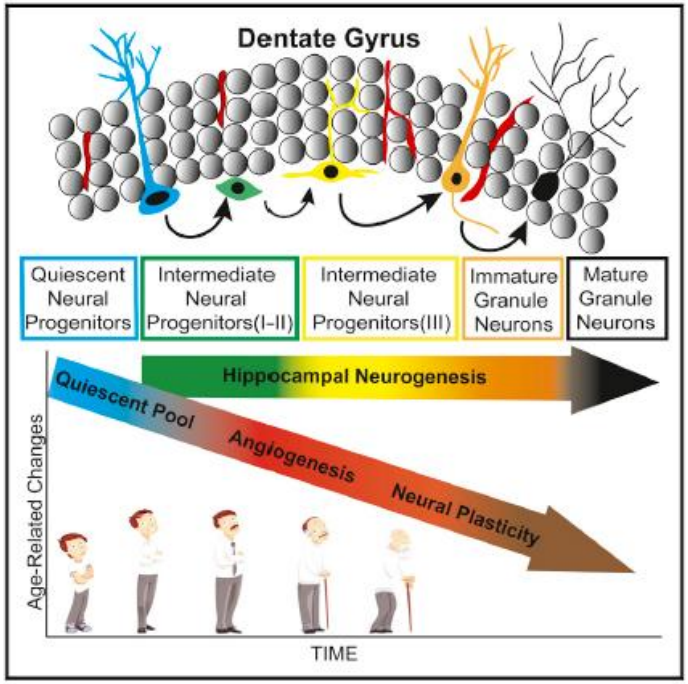
Human tissue collection
28 postmortem hippocampal tissue samples derived from healthy adults
14-79 years of age

Short Article

Cell Stem Cell

Human Hippocampal Neurogenesis Persists throughout Aging

Graphical Abstract



Authors

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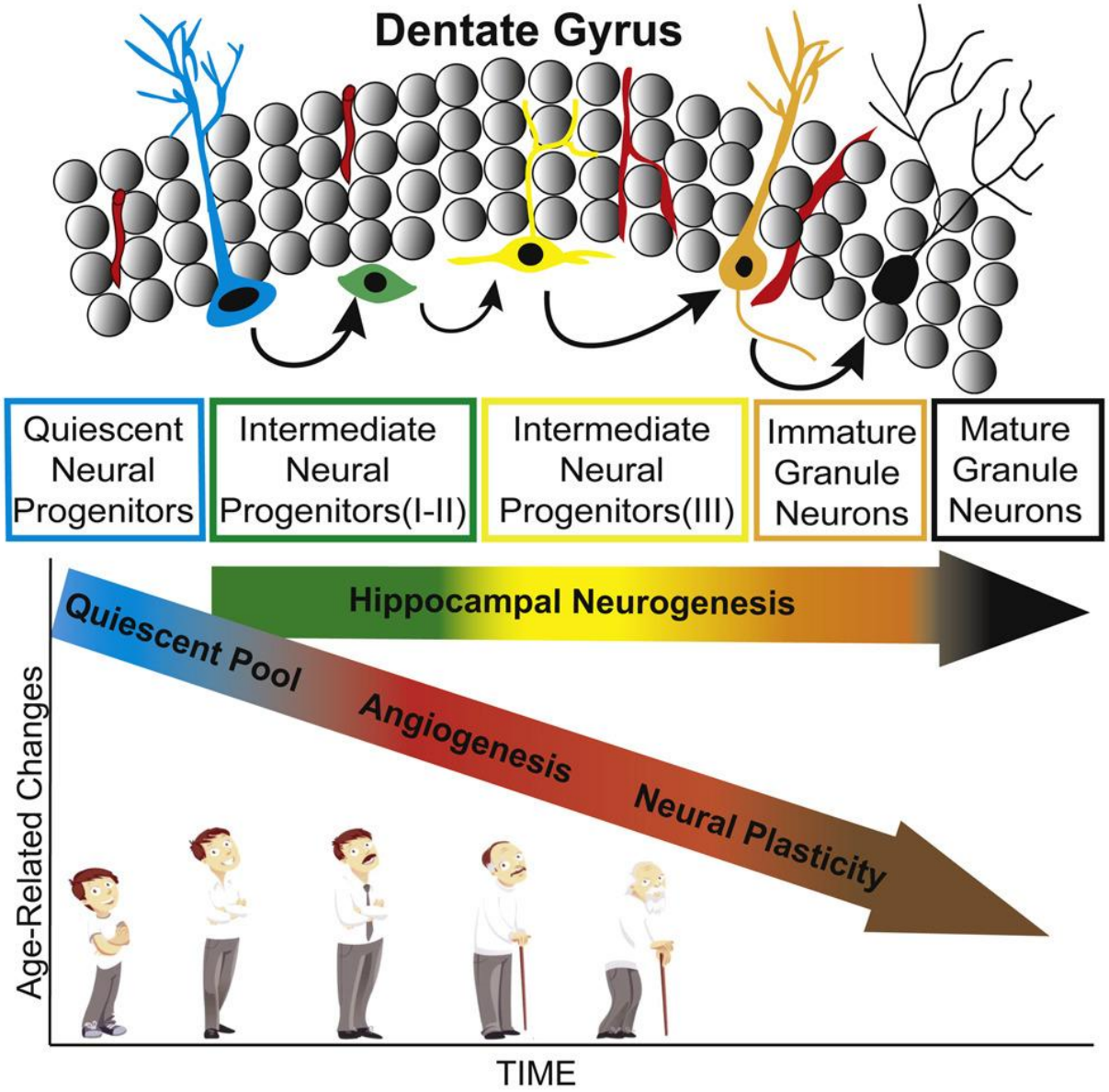
In Brief

Boldrini et al. find persistent adult neurogenesis in humans into the eighth decade of life, despite declines in quiescent stem cell pools, angiogenesis, and neuroplasticity. Over a 65-year age span, proliferating neural progenitors, immature and mature granule neurons, glia, and dentate gryus volume were unchanged.

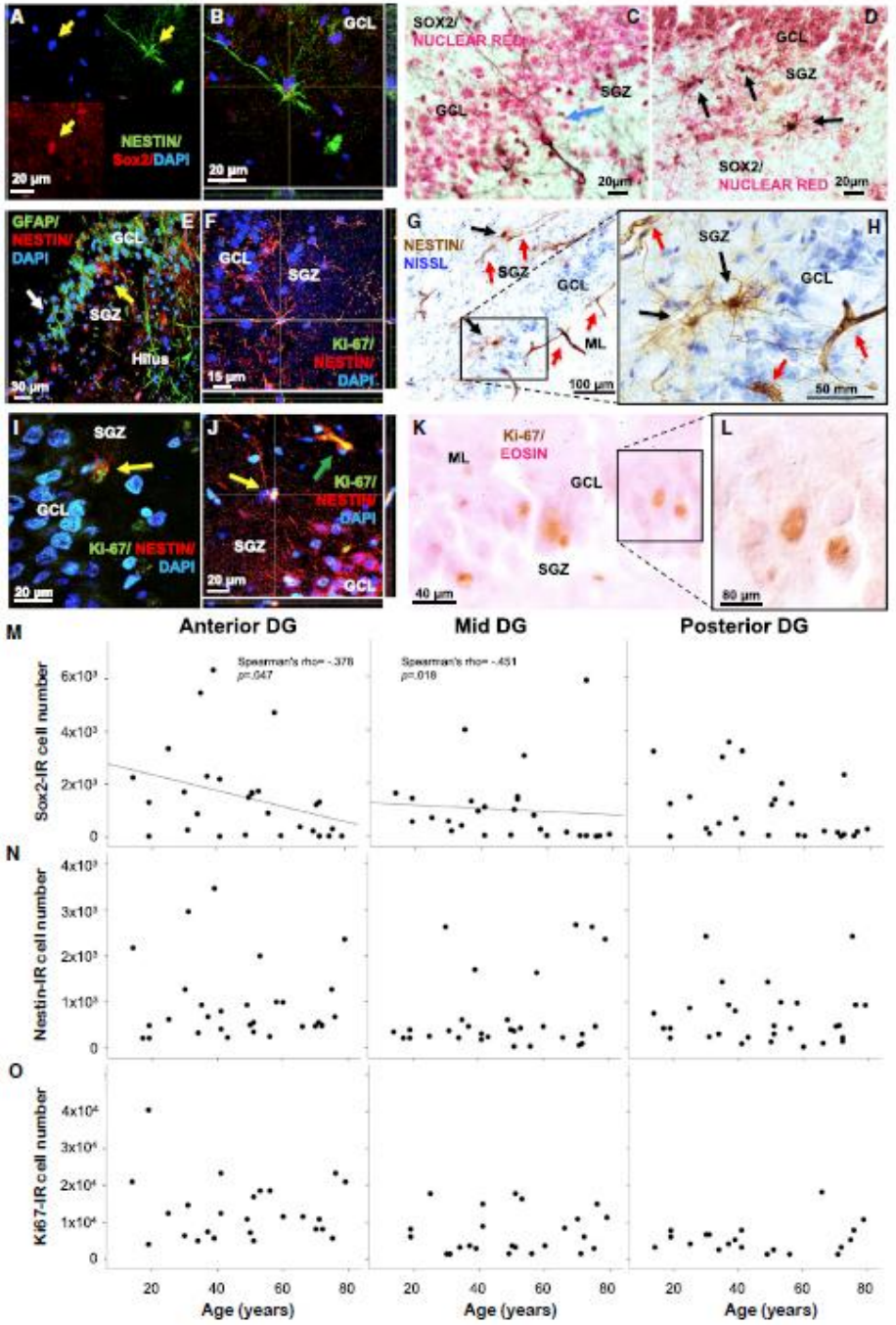
Highlights

- Pools of quiescent stem cells are smaller in aged human hippocampal dentate gyri
- Proliferating progenitor and immature neuron pools are stable with aging
- Angiogenesis and neuroplasticity decline in older humans
- Granule neurons, glia, and dentate gryus volume are unchanged with aging

Even old brains can make new neurons…
But new neurons in older brains may make fewer connections



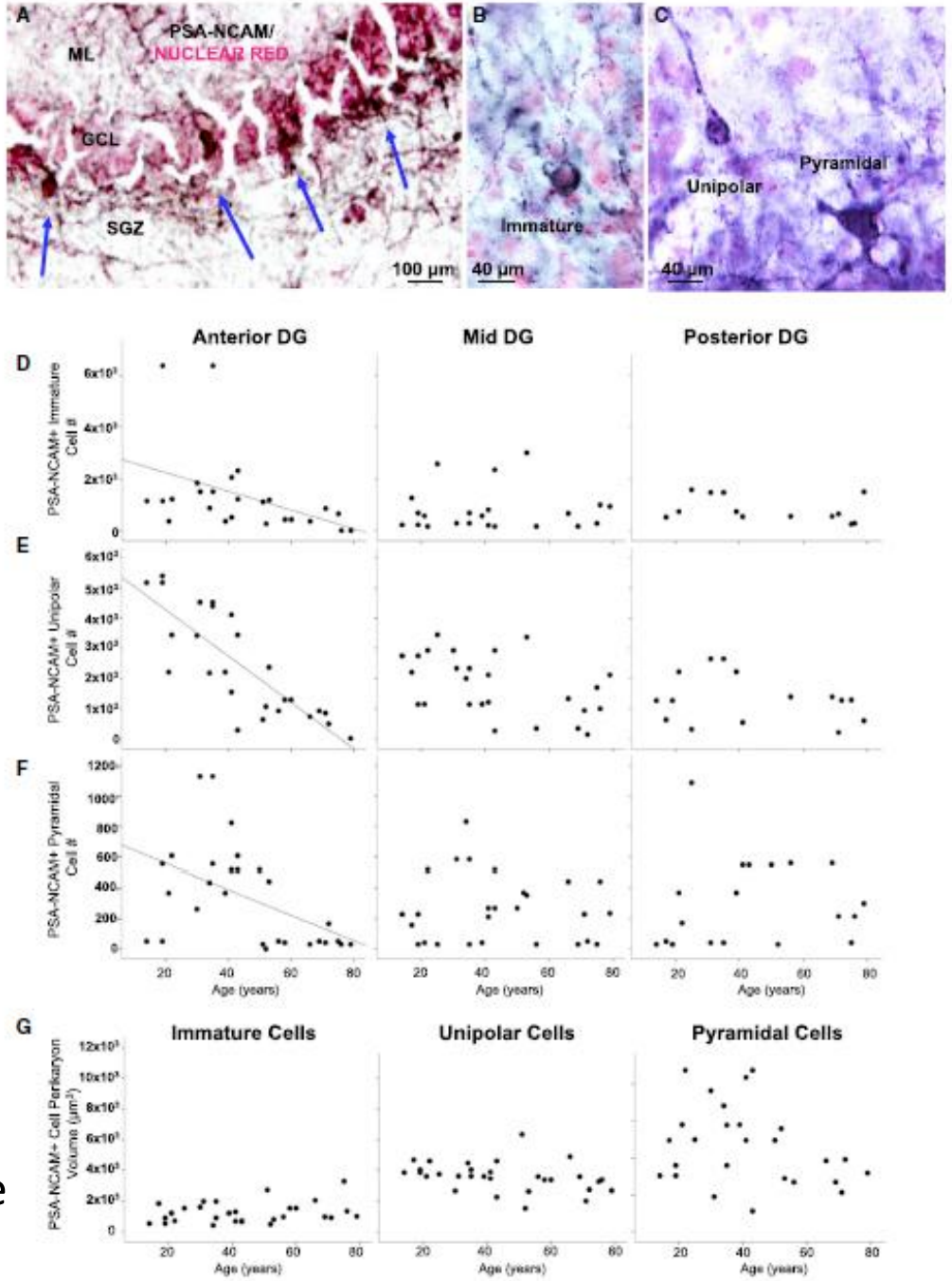
Fewer Quiescent Neural Progenitors and Stable Proliferating Intermediate Neural Progenitors in Aging Human Dentate Gyrus



- **Sox2+ QNP pool was smaller** in the anterior-mid DG of older people
- **Nestin+ and Sox2/Nestin+ INP type I-II cells were not fewer in older humans** in anterior, mid or posterior DG
- **Ki-67+ cells unchanged** between 14 and 79 years of age

Fewer PSA-NCAM+ cells in aging human DG

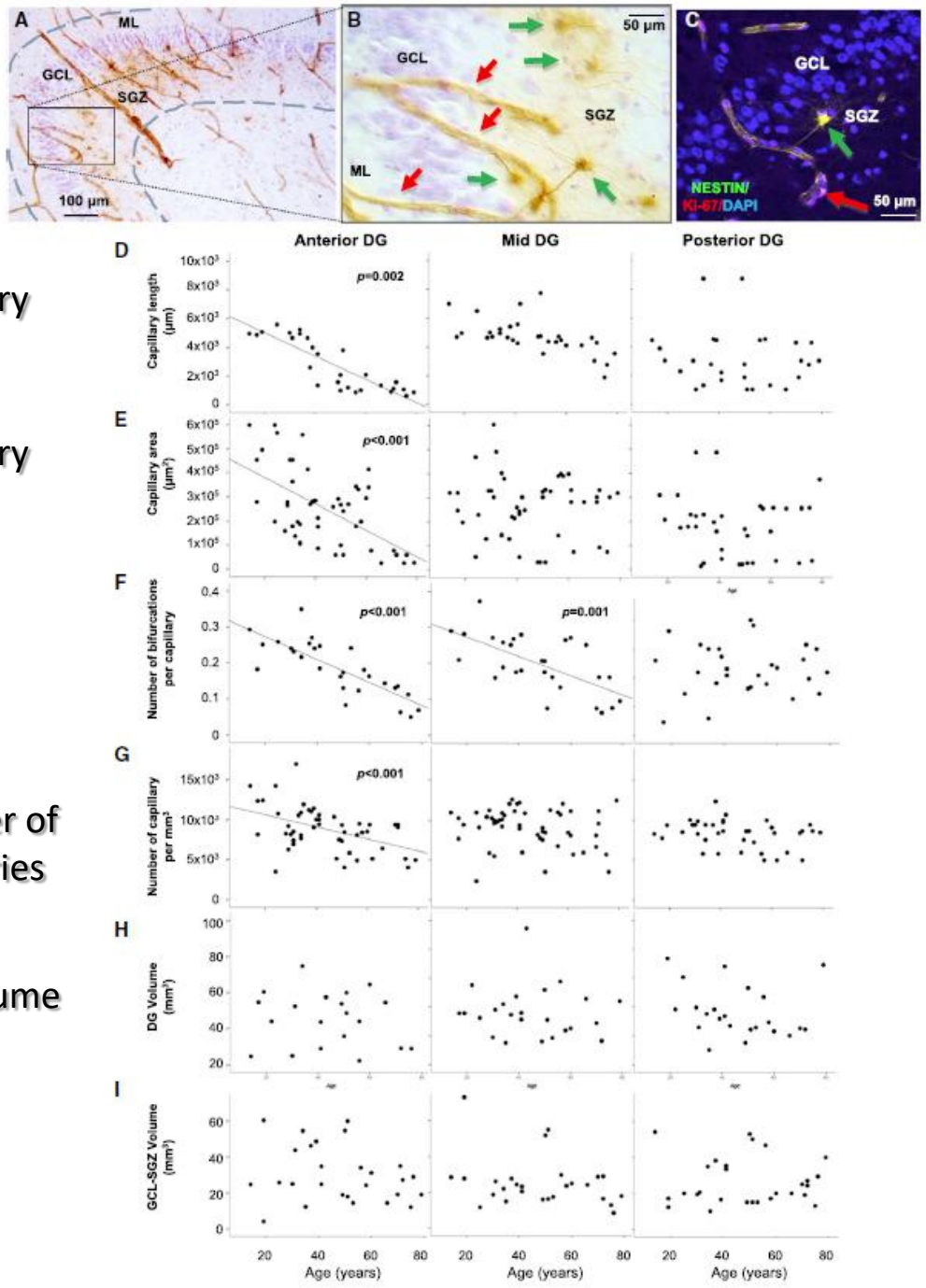
⇒ Decline in neuroplasticity



- PSA-NCAM was detected in neural cells with **immature, bipolar, and pyramidal morphology**
- PSA-NCAM/DCX marker of **neuroblasts**
- PSA-NCAM marker of **neuroplasticity**
- PSA-NCAM+ mature GNs were all **fewer in anterior DG** with older age

Age-associated DG angiogenesis decline and stable DG volume

- **smaller** total capillary area and length and **shorter** and **less** branched capillaries correlating with **fewer** PSA-NCAM+ cells selectively in anterior-mid DG



To sum up…

- Pools of **quiescent stem cells are smaller** in aged human hippocampal DG
- **Proliferating progenitor and immature neuron pools are stable** with aging
- The older brains had **less vascular development**
- The neurons in older hippocampi expressed **lower levels of proteins associated with plasticity, or the formation of new neural connections**
- Granule neurons, glia, and DG volume are **unchanged** with aging
- **Young and old brains produce thousands of new neurons, but neurons might be less able to form connections in old brains**

Adult human hippocampal neurogenesis exists or not?

Controversy, evidence and remaining questions…

CellPress
REVIEWS

Spotlight

Adult Human Hippocampal Neurogenesis: Controversy and Evidence

Hyunah Lee[1] and Sandrine Thuret[1,*]

The hippocampus has been described as one of the few sites in the mammalian brain capable of generating new cells continuously throughout life. Two recent studies that report contradicting findings on adult human hippocampal neurogenesis, however, reminds us of the caveats and challenges of studying this phenomenon in post-mortem tissues.

proliferating cells and young immature neurons during the first year of life in the dentate gyrus (DG), which is known to be the primary site of adult hippocampal neurogenesis. In line with existing literature [5,6], the authors reported a sharp age-dependent decrease in the number of these cells. Only a few isolated young neurons were observed by 7 and 13 years of age. No young neurons were detected in the DG of adult patients with epilepsy or healthy adults. A similar age-dependent reduction was also seen in rhesus macaques.

By contrast, Boldrini and colleagues [4] examined 28 postmortem hippocampal tissue samples derived from healthy adults 'without cognitive impairment, neuropsychiatric disease, or (history of medical) treatment' from 14 to 79 years of age. The authors used similar immunohistochemistry methods as Sorrells and colleagues did to visualize various cell

quiescent neural stem cells (GFAP/Sox2/Nestin+), which showed an age-dependent decrease specifically in the anterior-mid DG. The authors also found that the DG volume remained largely unchanged, whereas measures for neuroplasticity and angiogenesis declined with age in the anterior DG. These concomitant decreases were also found to be significantly correlated with each other.

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Please cite this article in press as: Kempermann et al., Human Adult Neurogenesis: Evidence and Remaining Questions, Cell Stem Cell (2018), https://doi.org/10.1016/j.stem.2018.04.004

Cell Stem Cell

Minireview

CellPress

Human Adult Neurogenesis: Evidence and Remaining Questions

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https://doi.org/10.1016/j.stem.2018.04.004

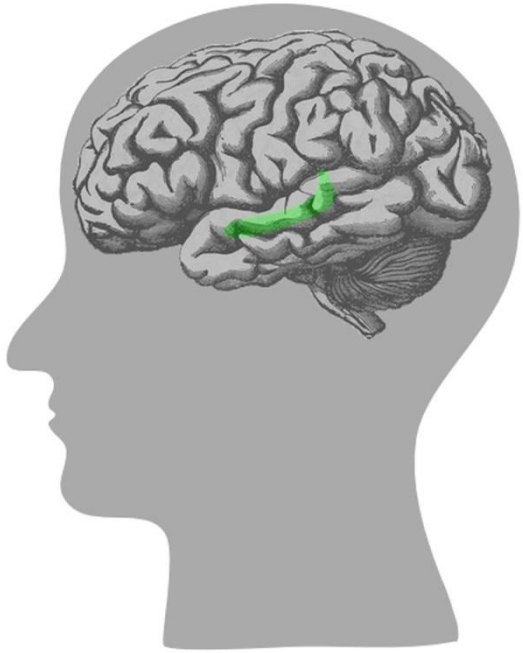
Renewed discussion about whether or not adult neurogenesis exists in the human hippocampus, and the nature and strength of the supporting evidence, has been reignited by two prominently published reports with opposite conclusions. Here, we summarize the state of the field and argue that there is currently no reason to abandon the idea that adult-generated neurons make important functional contributions to neural plasticity and cognition across the human lifespan.

Key evidence

Birthdating study with **BrdU**
N = 5
Eriksson et al. 1998

Birthdating study with **IdU**
N = 4
Ernst et al. 2014

Birthdating study with **14C**
N = 55
Spalding, Bergmann et al. 2013



Proposed functional contribution

- Temporal and spatial contextualization of information
- Avoidance of catastrophic interference, "behavioral pattern separation"
- Flexible integration of new information into pre-existing contexts
- Forgetting
- Affective behaviors

Spatial navigation, Episodic memory, Autobiographic memory, Adaptability to novel contexts

Isolation of neurogenic precursor cells
4 reports,
e.g. Palmer et al. (2001)

Proxy marker studies in disease cases

> 10 reports, *see main text for references* X

Marker panel study

Knoth et al., 2010
Boldrini et al., 2018 X

Supporting evidence

X, conflicting report

- **Technical issues:**

  the limitations of marker studies

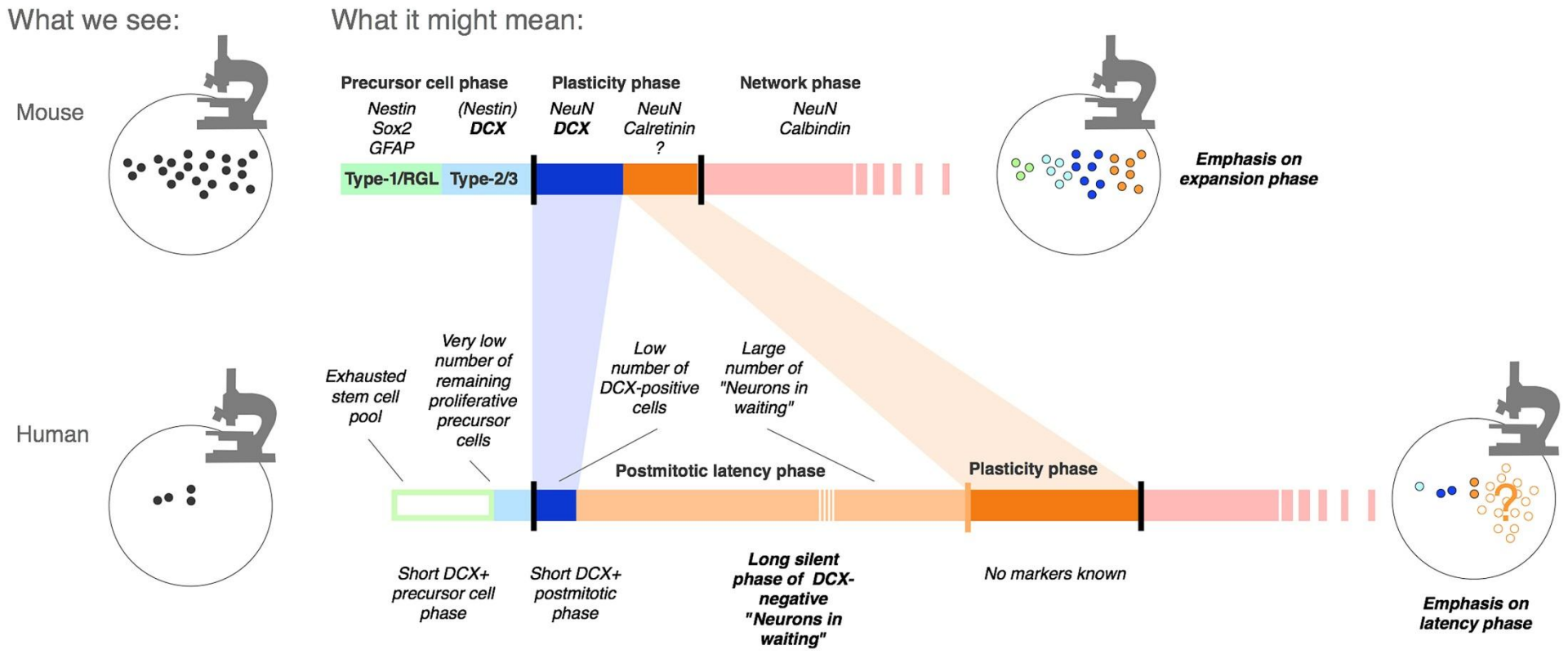
  quantitative aspects (stereology)

- **Conceptual contexts**

  potential species differences (fig.)

  functional aspects

  evolutionary considerations


What we see:
What it might mean:
Mouse
Human
Precursor cell phase
Plasticity phase
Network phase
Nestin
Sox2
GFAP
(Nestin)
DCX
NeuN
DCX
NeuN
Calretinin
?
NeuN
Calbindin
Type-1/RGL
Type-2/3
Emphasis on expansion phase
Exhausted stem cell pool
Very low number of remaining proliferative precursor cells
Low number of DCX-positive cells
Large number of "Neurons in waiting"
Postmitotic latency phase
Plasticity phase
Short DCX+ precursor cell phase
Short DCX+ postmitotic phase
Long silent phase of DCX-negative "Neurons in waiting"
No markers known
Emphasis on latency phase

- different mammalian species might have developed different solutions to the problem of how to provide a **critical population of highly plastic cells** to the network
- the **balance between retained neurogenic potential from proliferating progenitor cells or from a reservoir of pre-generated, highly excitable cells** might also vary between human individuals
- this balance is likely to change across the lifespan
- If the duration of the window of plasticity lengthens with age, **extremely low numbers of proliferating cells could still contribute to a reservoir of plastic cells that sustain the required functionality**
- the process of adult neurogenesis may somewhat parallel what occurs in the female reproductive system of mammals, where all stem cell proliferation that generates the population of egg cells occurs very early in life
- there might also be a **"neurogenic menopause,"** in which the potential is used up, and this might indeed contribute to age-related cognitive decline

- *There is currently no reason to abandon the idea that adult-generated neurons make important functional contributions to neural plasticity and cognition across the human lifespan.*

- *There is a clear need for additional ways to study the generation of new neurons in adult humans.*

Thank you