Vieillissement du cerveau et cellules souches neurales

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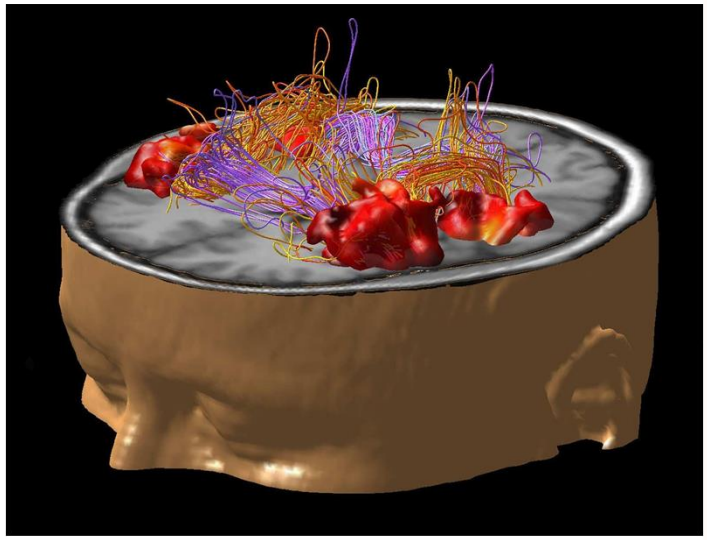
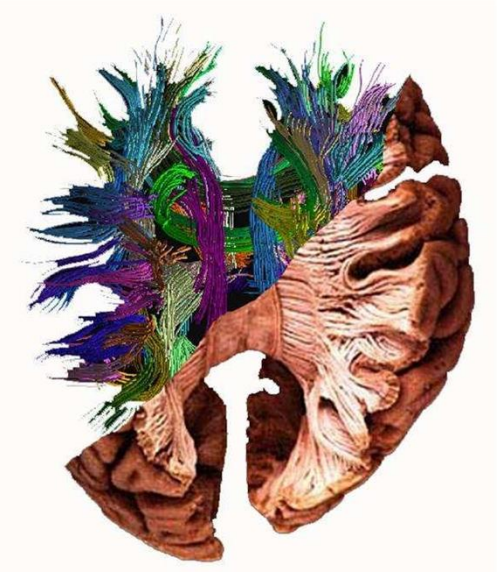
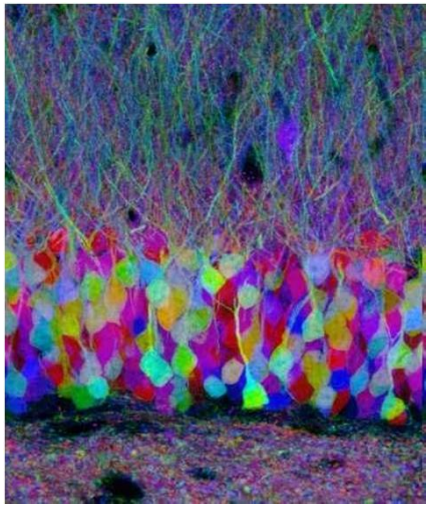
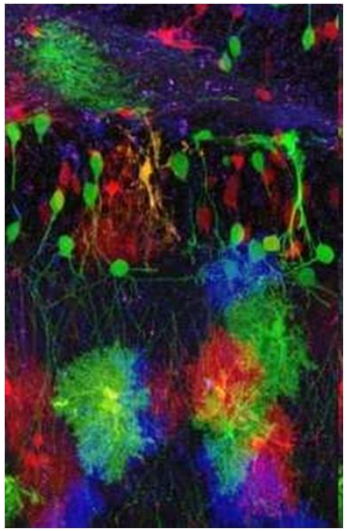
Complexité du système nerveux





180 000 km
de fibres
myélinisées





10^{11} neurones
10^{12} cellules gliales

10000 types de neurones

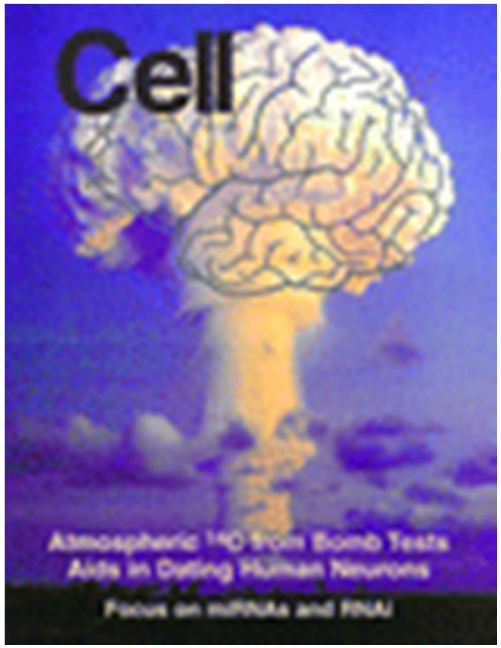
Une nouvelle Complexité:

les cellules souches et progénitrices adultes

We are born with a certain number of brain cells which decrease with age. Everything must die in the brain or spinal cord - nothing can regenerate.

Ramon y Cajal 1902

La datation au ^{14}Carbone des neurones montre que le stock de neurones nôest pas renouvelé au cours de lôexistence



Essais atomiques

Les neurones du cerveau ont la quantité de 14C dôavant les essais atomiques

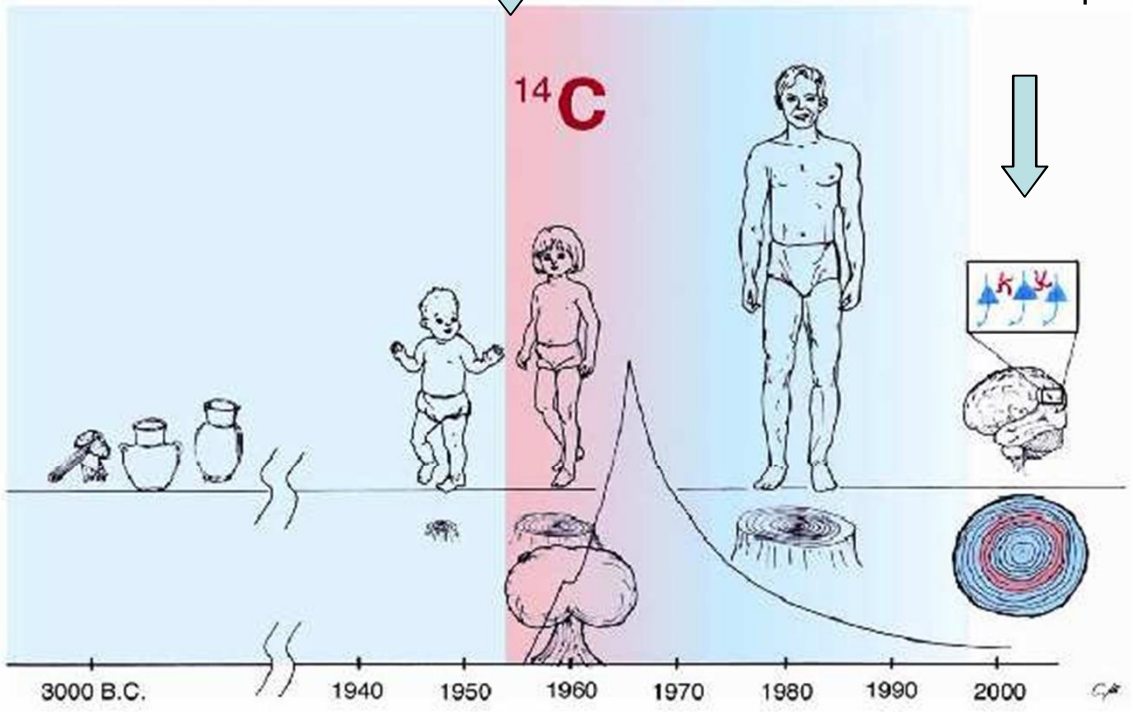


Figure 1. Retrospective Birth Dating of Human Neurons

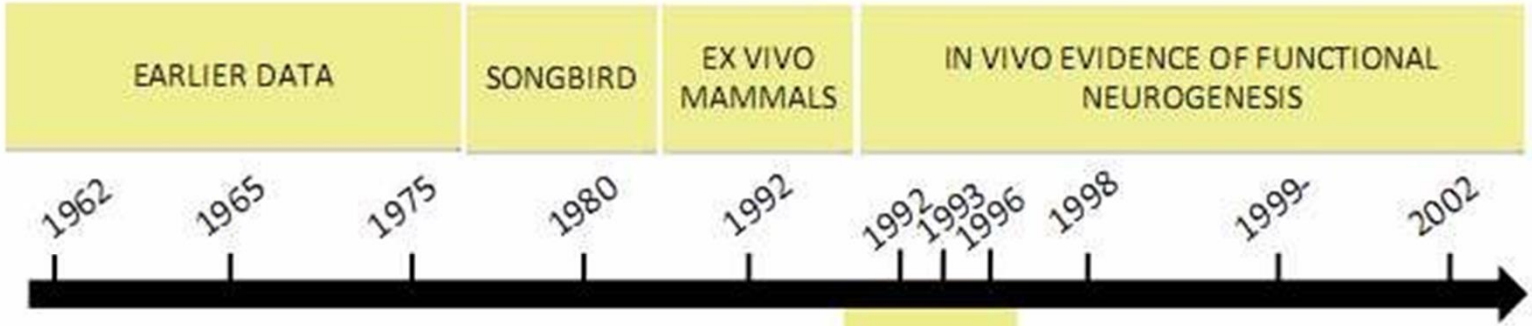
The amount of ^{14}C in neurons of the human cerebral cortex (blue) corresponds to the amount of ^{14}C found in the atmosphere at the time of birth of the individual. This shows that there is minimal turnover of neurons during postnatal and adult life. Nonneuronal cells are younger, as shown by higher levels of ^{14}C (red). The amount of ^{14}C in the atmosphere corresponds to the amount found deposited in the rings of pine trees in Sweden, the geographic area studied (Spalding et al., 2005). Illustration by Claudio Mare, Somerville, Massachusetts.

Les exceptions à la règle

Une nouvelle Complexité:

les cellules souches et progénitrices adultes

Historical overview on adult neurogenesis in Vertebrates



1962	1965	1975	1980	1992	1992 1993 1996	1998	1999	2002
Altman	*Altman and Das*	*Kaplan and Hinds*	*Nottebohm*	*Weiss Bartlett*	*Van der Kooy, Buylla*	*Eriksson, Gage*	*Frisen Alvarez-Buylla Van der Kooy Bartlett*	*Gage*
Are new neurons formed in the rat brain?	Evidence of postnatal hippocampal neurogenesis in rats.	New neurons in olfactory bulbs and dentate gyrus in adult rat	Neurogenesis in the song-birds brain	*Bona fide* NSC isolated from adult brain and SVZ	SVZ cells die or selfrenew SVZ cells are multipotent in mouse Rostral migration, as chain through the RMS	New neurons in adult human hippocampus	The adult neural stem cell: is an ependymal or subependymal cell?	Newly generated cells are functional neurons.

Are New Neurons Formed in the Brains of Adult Mammals?

JOSEPH ALTMAN
Psychophysiological Laboratory, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Science, 1962

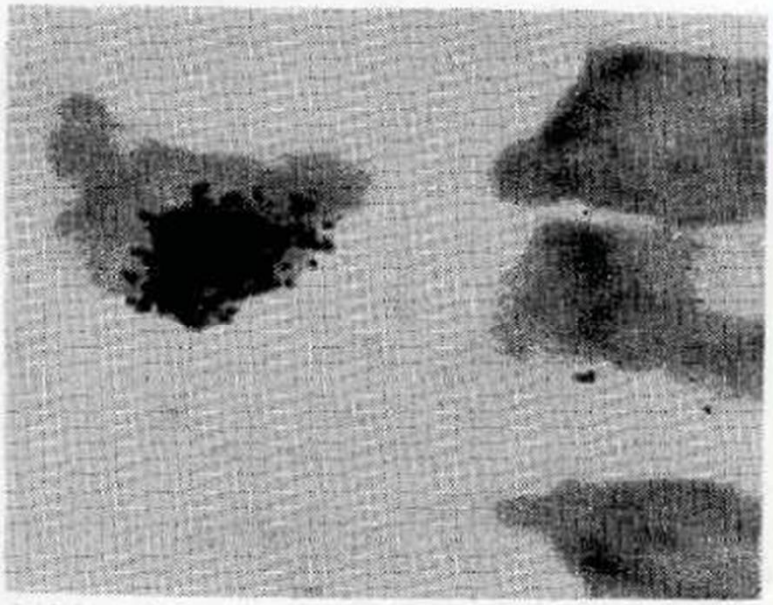


Fig. 2. Radioactive labeling of a neuron in the cerebral cortex of a rat which was sacrificed 1 month after the operation (about × 1170).

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

J. Comp Neurol, 1965

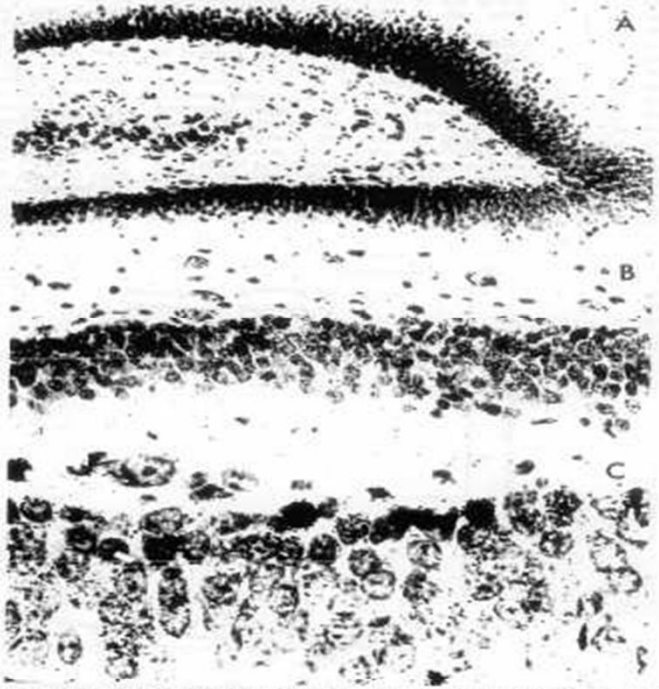
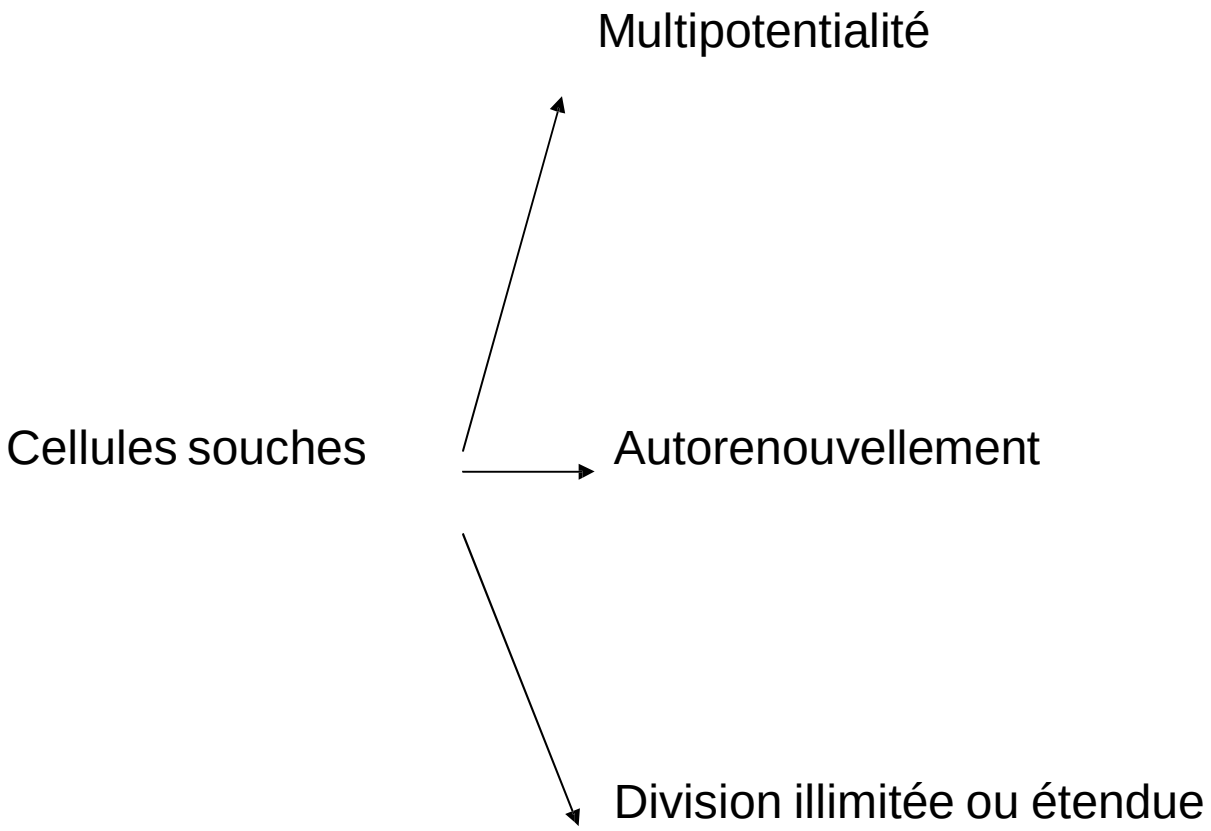


Fig. 1 Low and high power microphotographs of autoradiograms from the area of the dentate gyrus of the hippocampus in a rat injected with thymidine-H³ at the age of ten days and killed two months after the injection. Note labeling of granule cells, predominantly in the internal border (basal surface) of the granular layer. A, 100 ×; B, 256 ×; C, 640 ×.

"We postulated that this hierarchic construction process endows the brain with stability and rigidity as well as plasticity and flexibility"

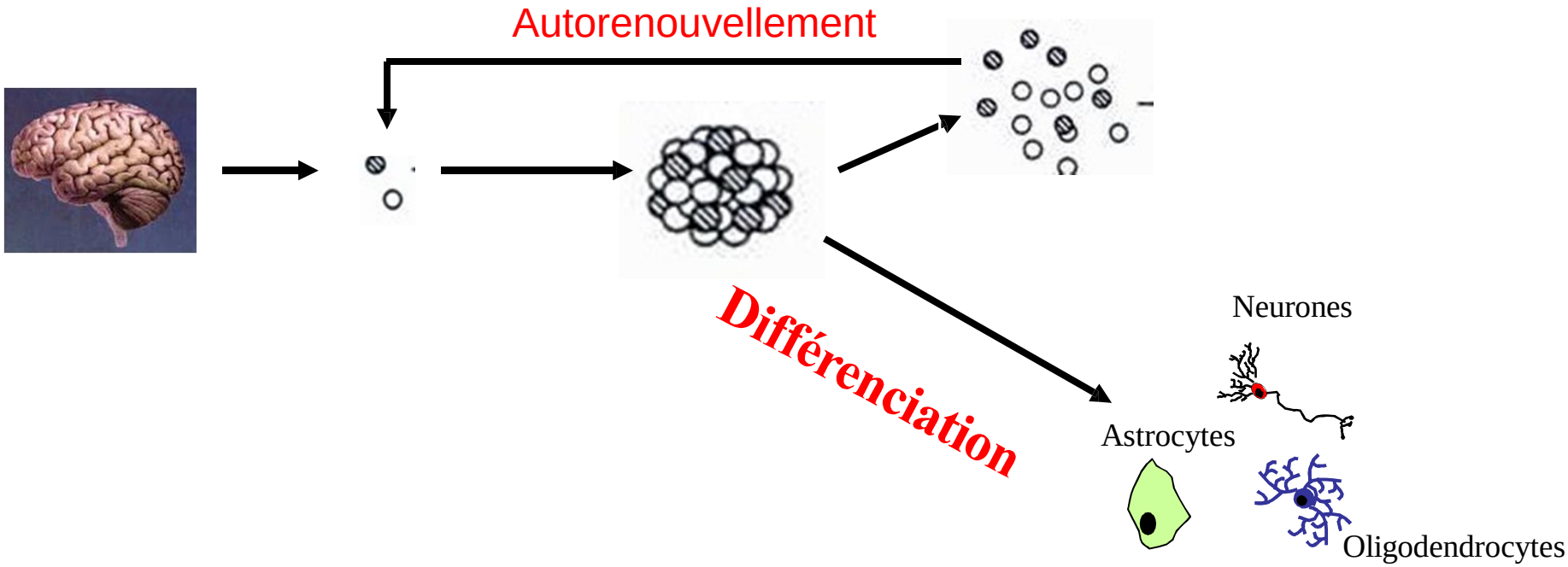
Propriétés des cellules souches



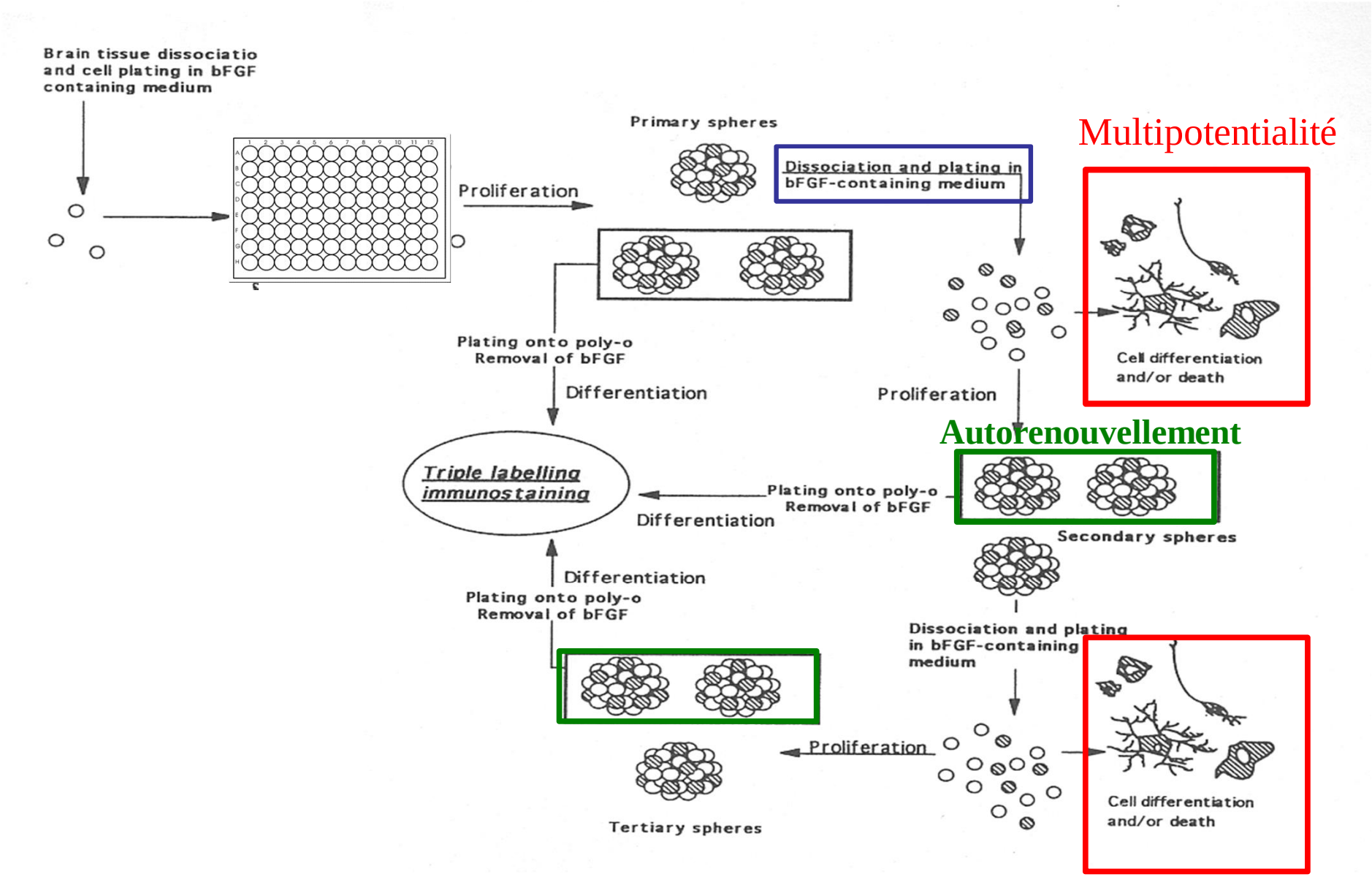
Mise en évidence de cellules souches in vitro

1992: détection dôune cellule souche neurale adulte chez la souris

1999: détection in vitro dôune cellule souche neurale adulte chez l ôhumain (age 15-87 ans)



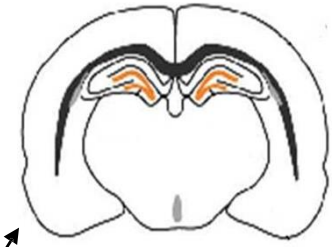
Mise en évidence: Les neurosphères



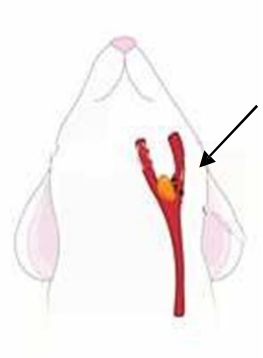
localisation des cellules souches et progénitrices neurales

Souris

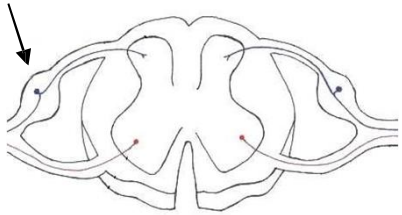
Zone sous ventriculaire



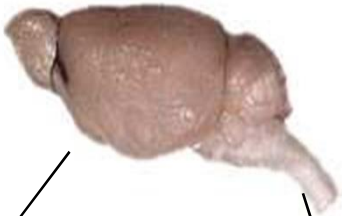
Hippocampe

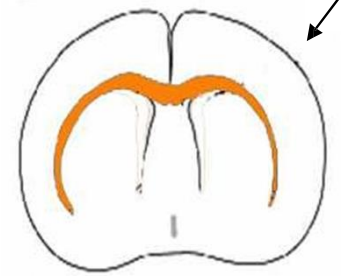


Corps carotidien

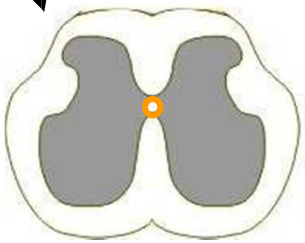


Ganglions rachidiens

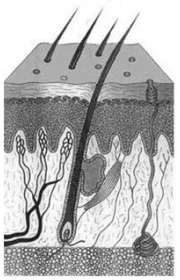




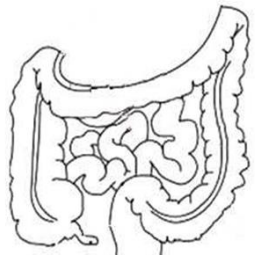
Région du corps calleux (progéniteurs)



Canal central de la moelle épinière

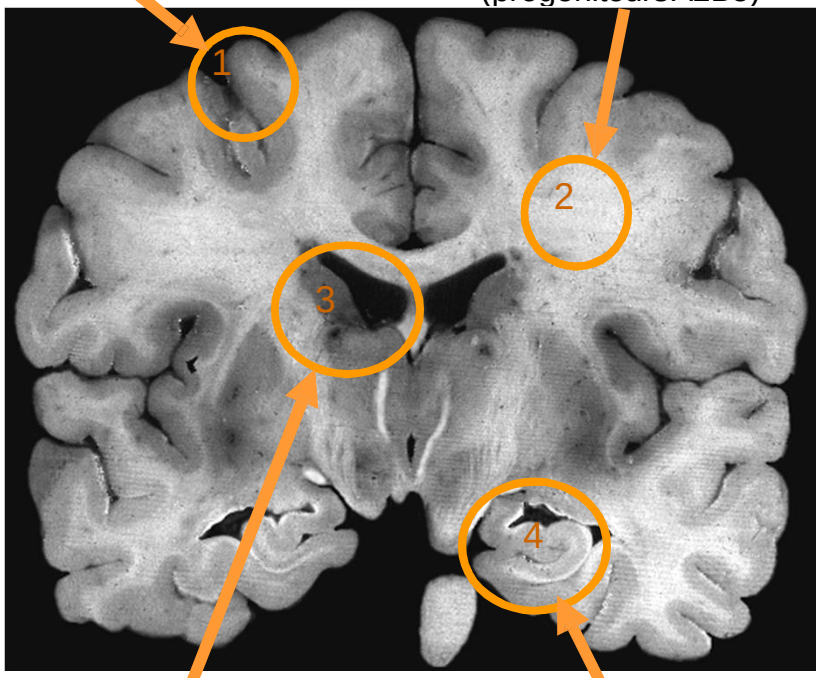


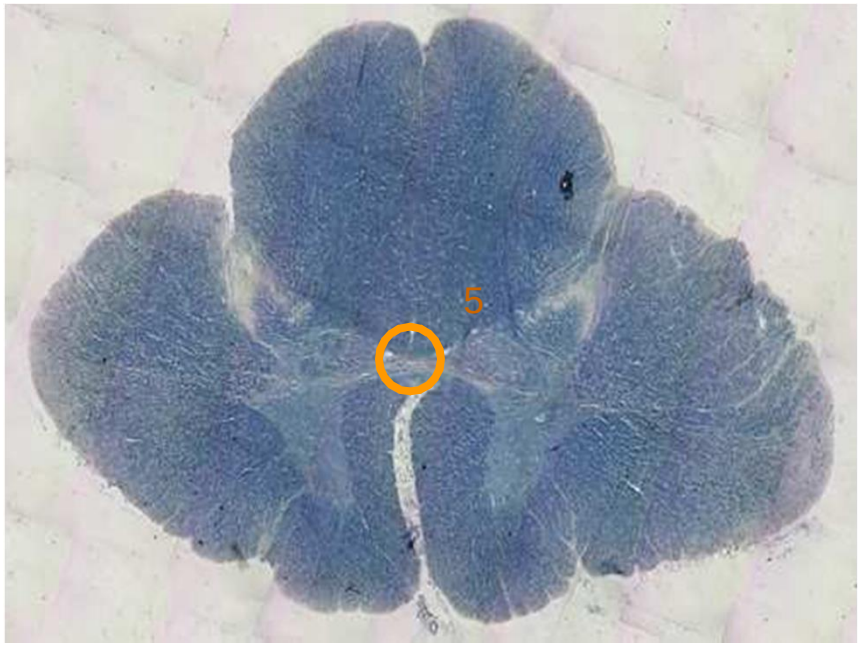
Peau



Système nerveux entérique (intestins)

Homme

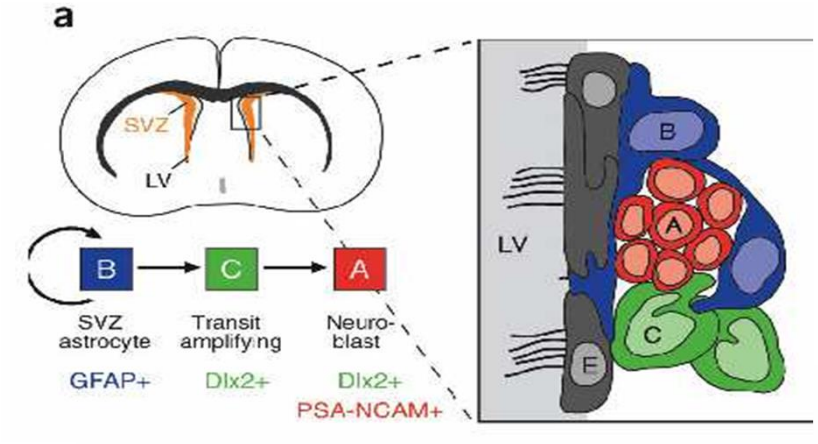




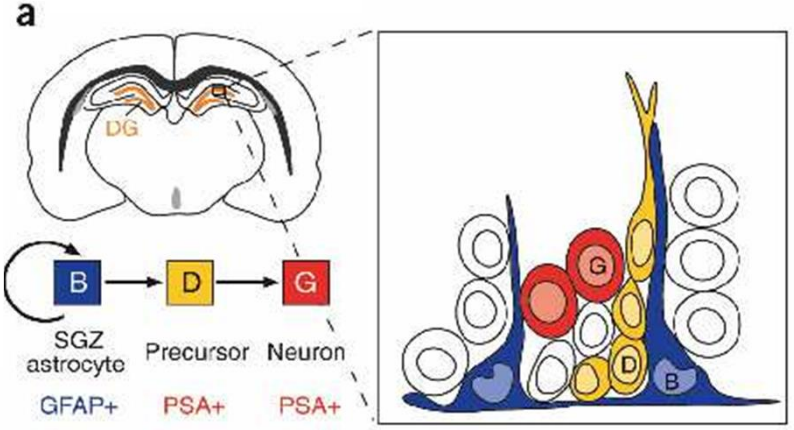
5-Canal central
de la moelle épinière
(progéniteurs)

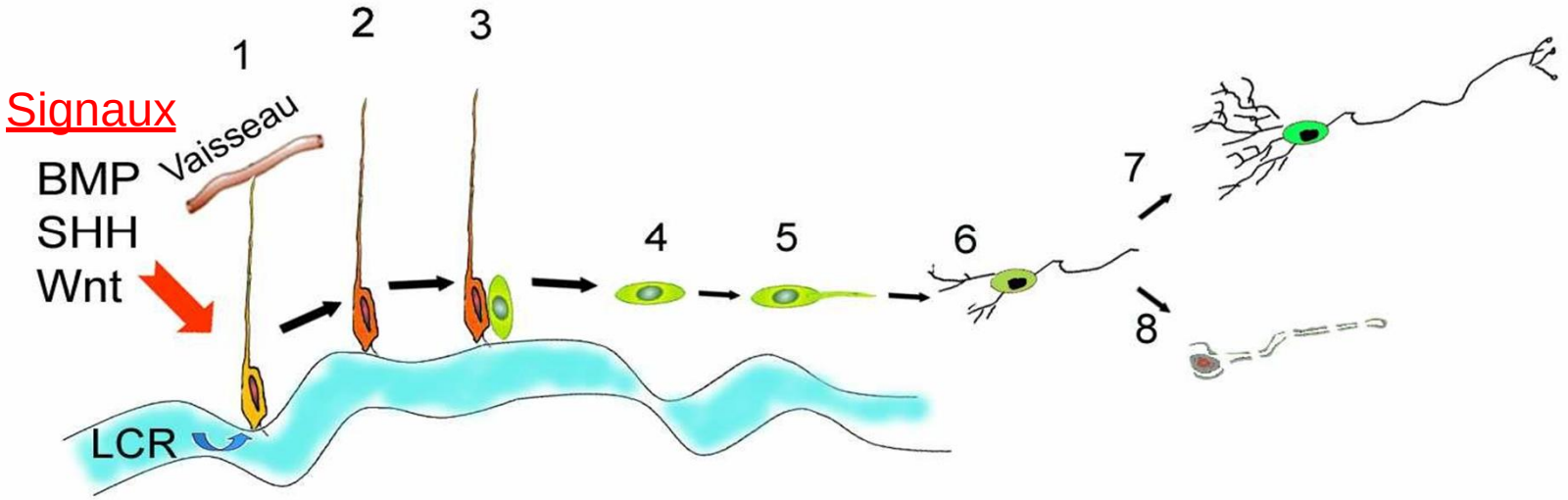
Des cellules souches neurales dans des niches

Zone sous ventriculaire

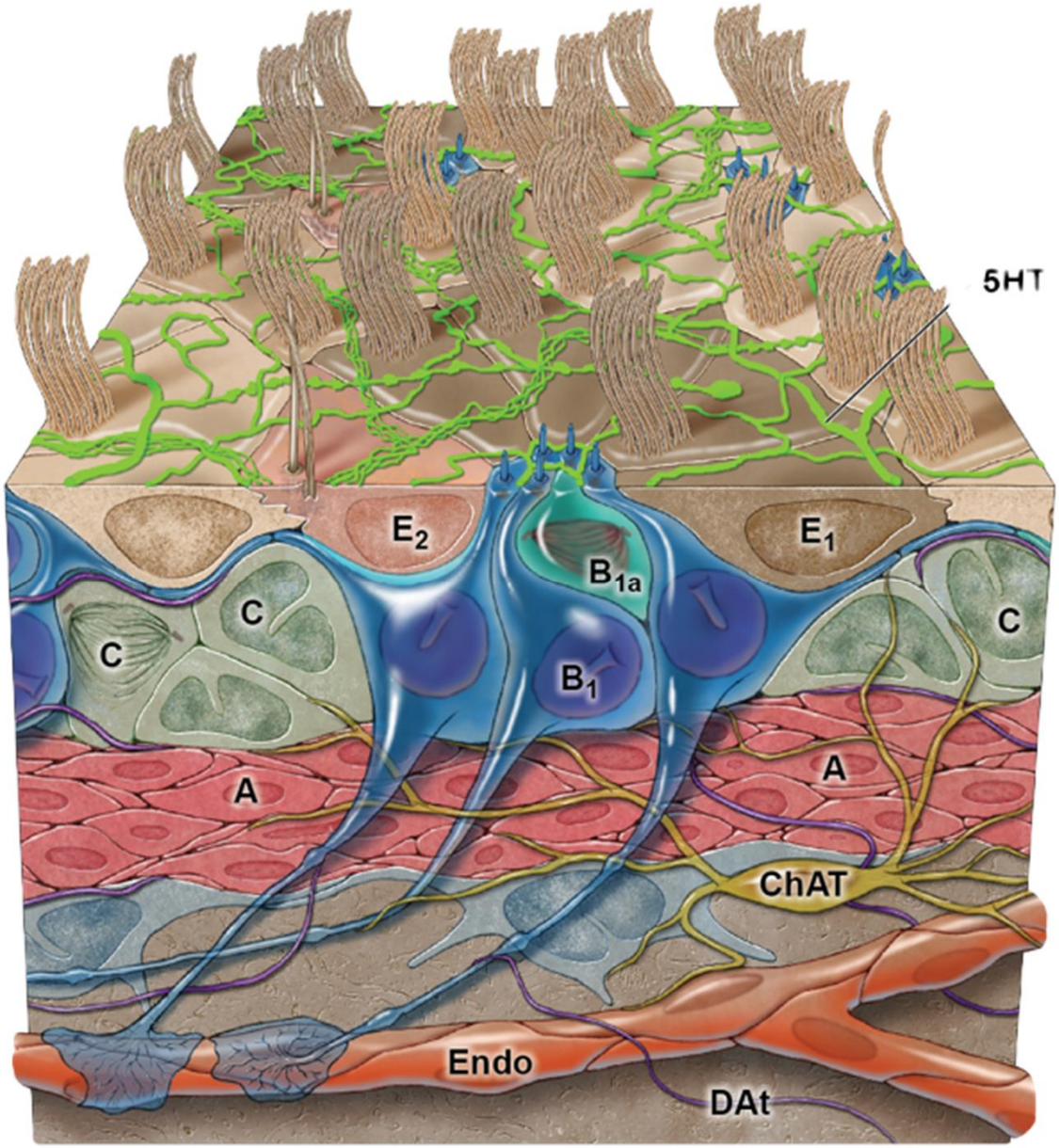


Hippocampe

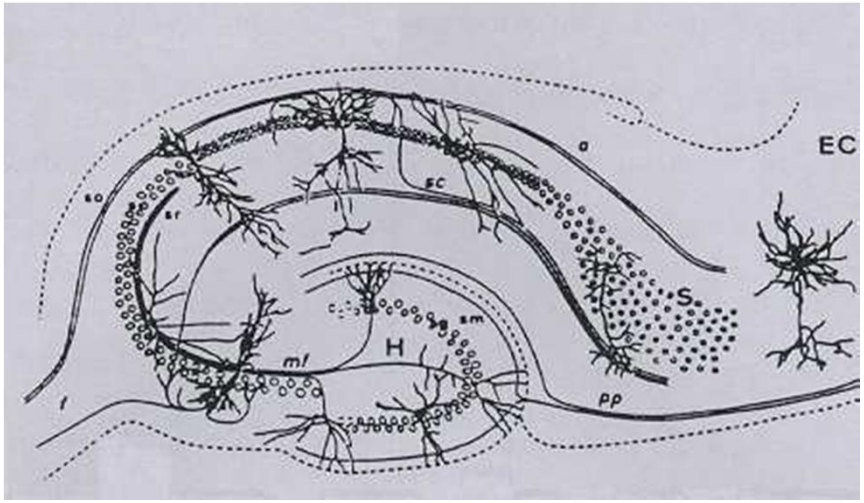


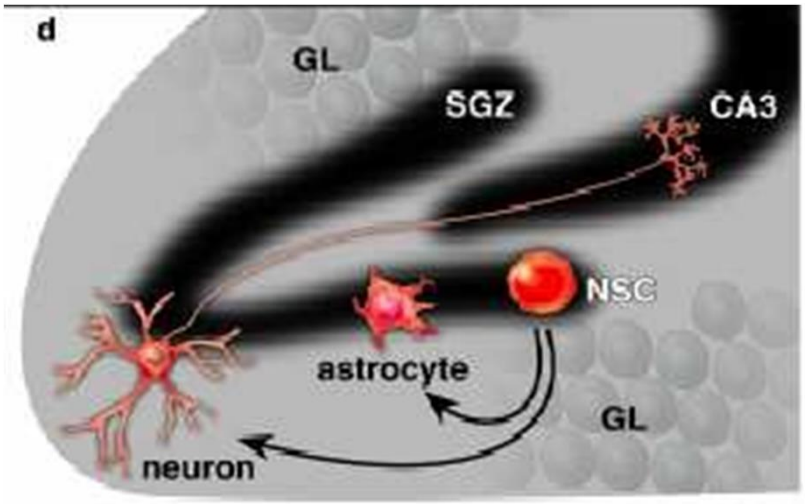


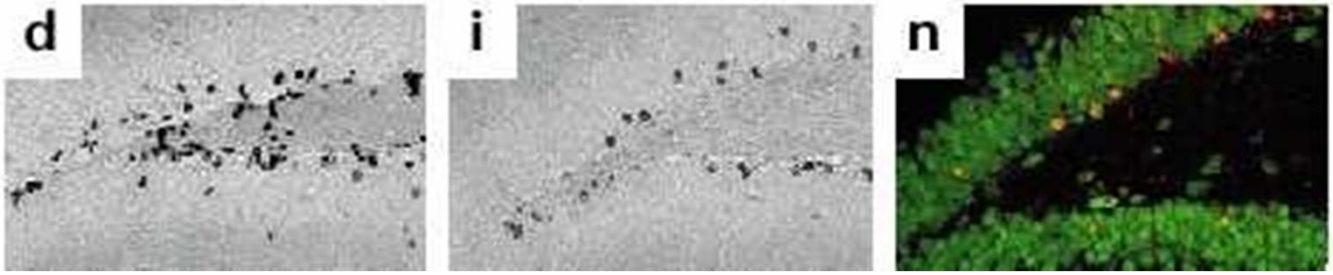
Niche de la zone sous ventriculaire



Neurogénèse dans l'hippocampe







Neurogénèse dans lôhippocampe

- 9,000 cellules par jours = 270,000/mois
- 20% des cellules totales du gyrus denté
- Maisé .. 50% meurent dans les 2 semaines après leur naissance
  - ñuse it or lose itò
- Un petit nombre de cellules survivent pendant qql mois

Quels rôles pour les neurogénèses adultes ?

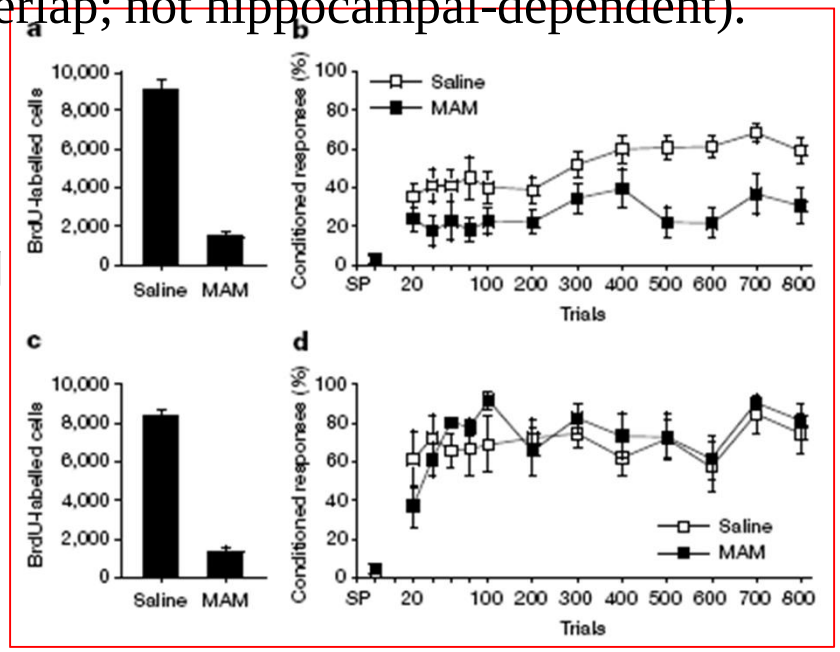
Hippocampal Neurogenesis in Memory Function:

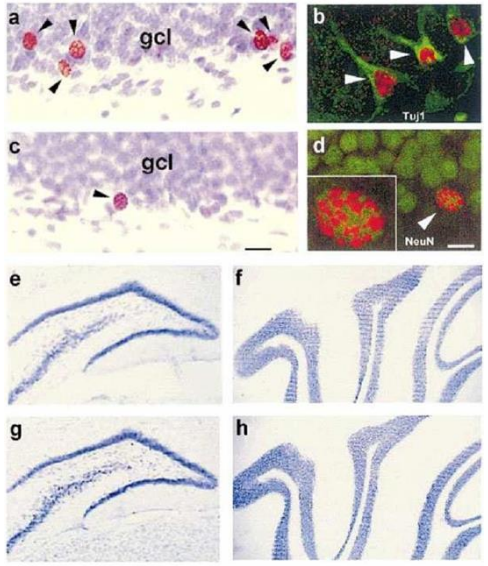
Shors, Gould et al 2001

- Disruption of adult neurogenesis with systemic methylazoxymethanol acetate (MAM) for 14 d.
- Classical conditioning of
  eyeblink: UCS = airpuff, CS
  = noise
  Trace (no overlap; hippocampal-dependent) versus
  Delay (overlap; ~~not hippocampal-dependent~~).

Trace Conditioning

Delay Conditioning

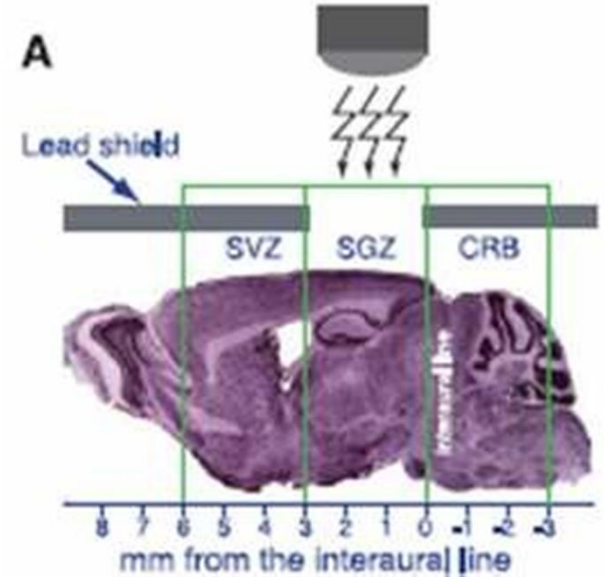


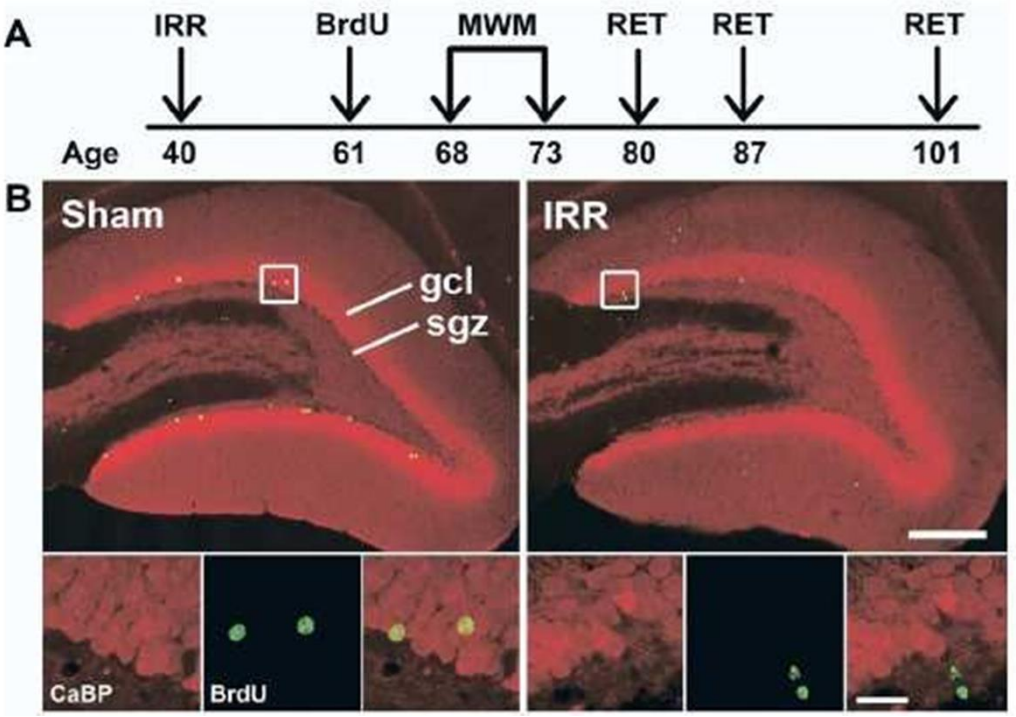


Hippocampal Neurogenesis in Memory Function:

Snyder et al., 2005

- Irradiation of Hippocampus.
- Long-term retention of spatial learning impaired.





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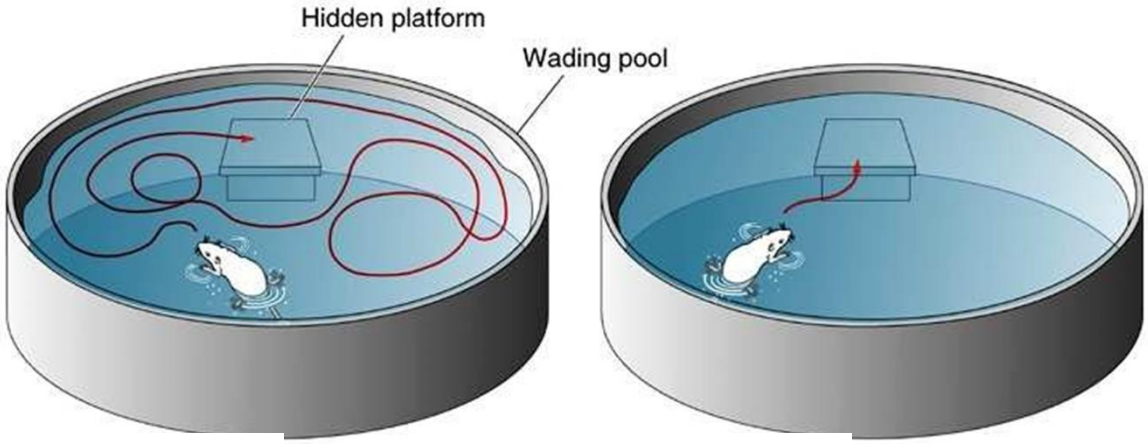
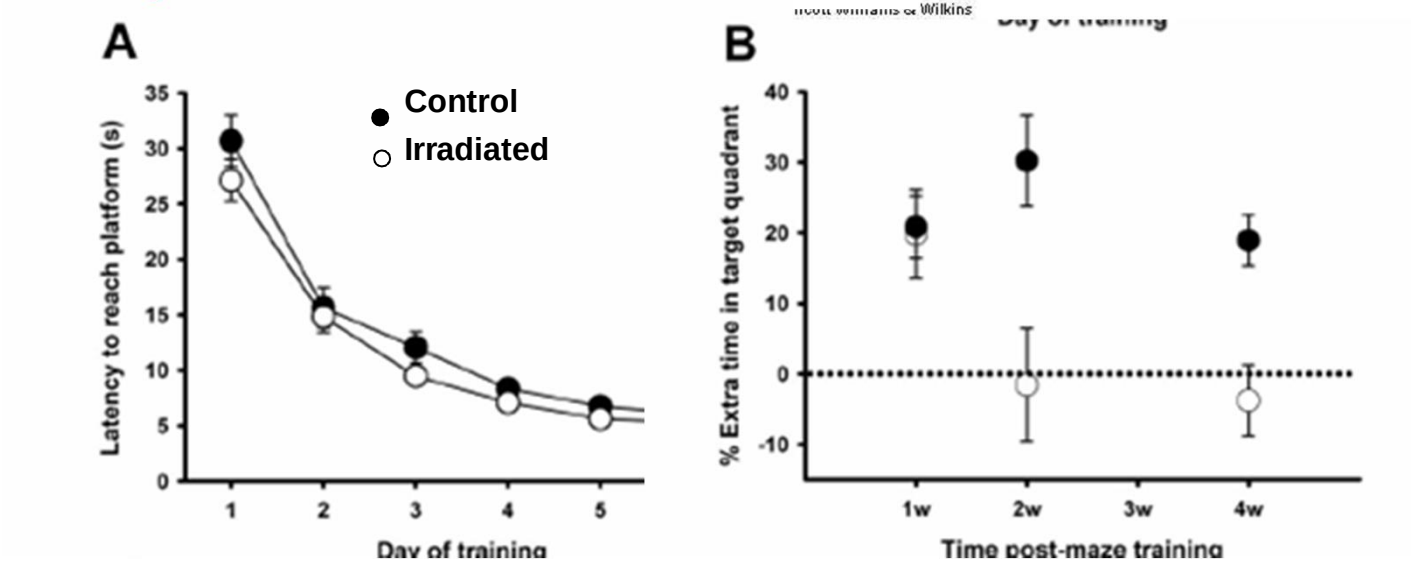
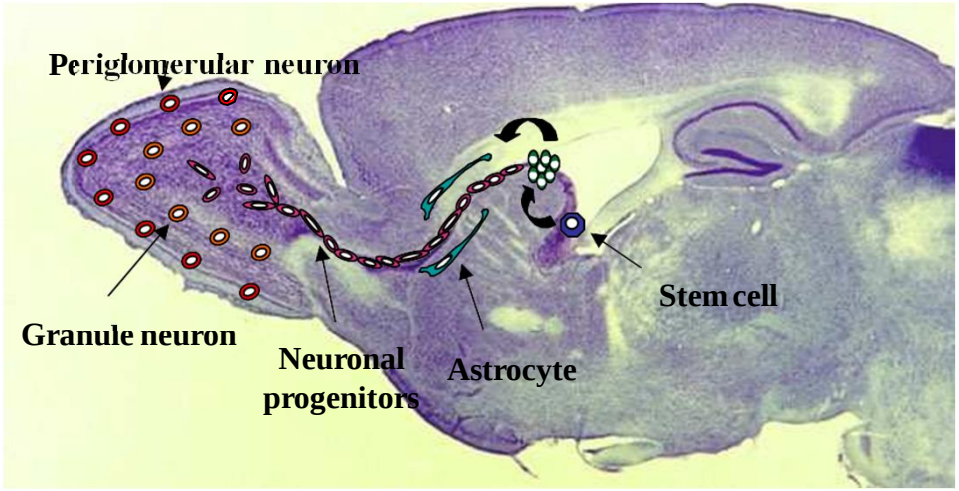


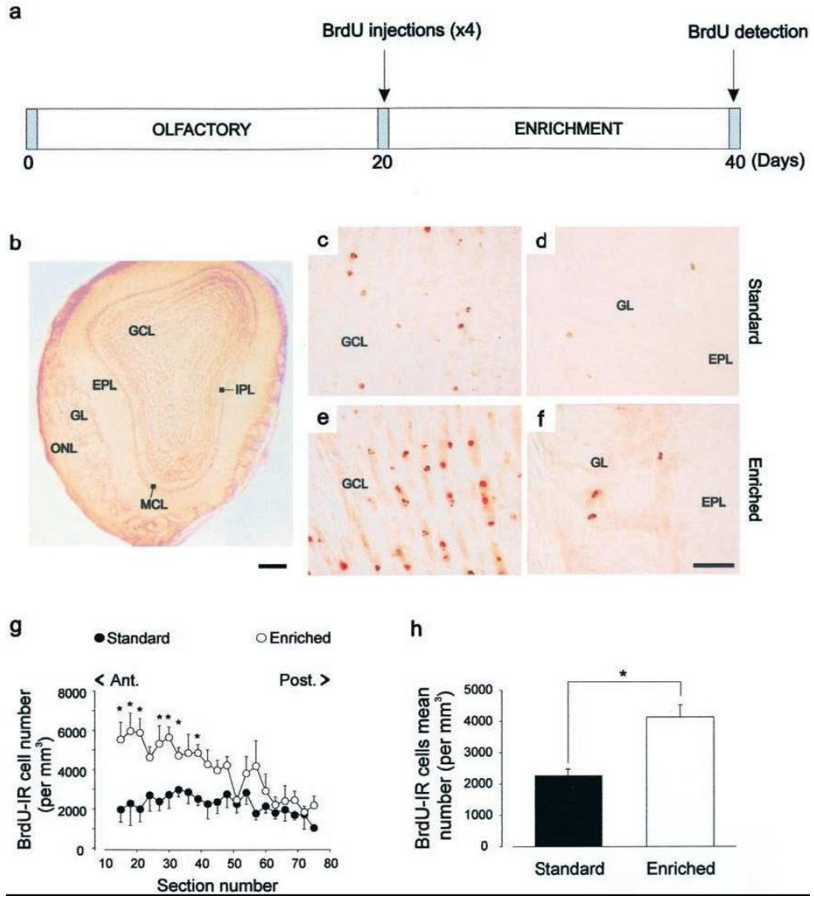
Acquisition **Retention**



Neurogénèse dans la zone sous ventriculaire chez les rongeurs

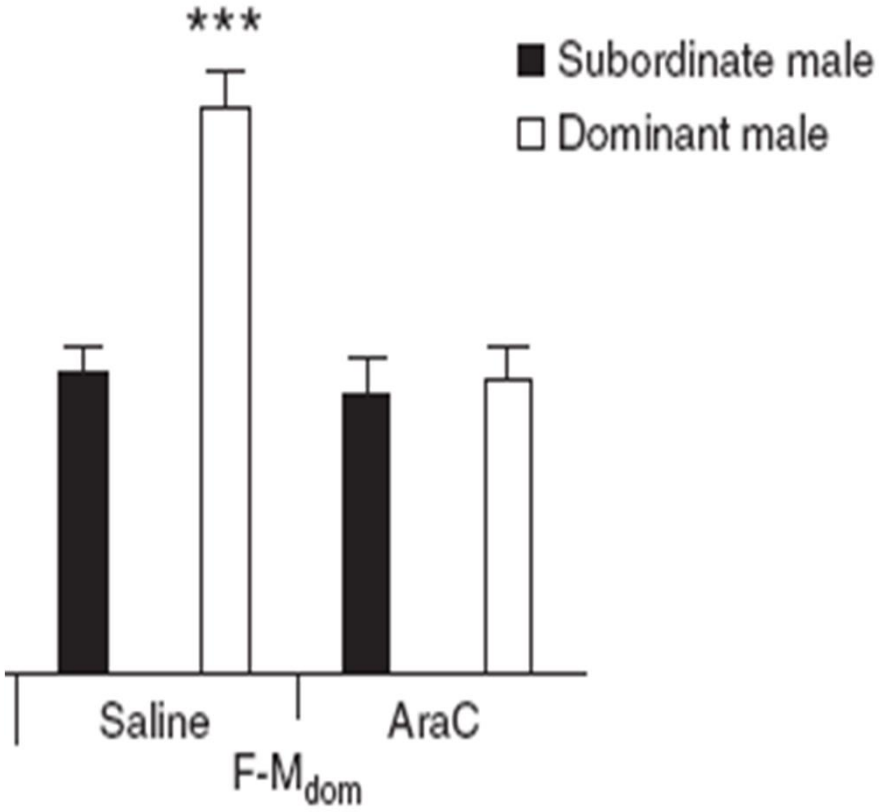


Migration rostrale des neuroblastes



Rochefort et al 2004

Réduction de la neurogénèse diminue l'attirance pour les males dominants.



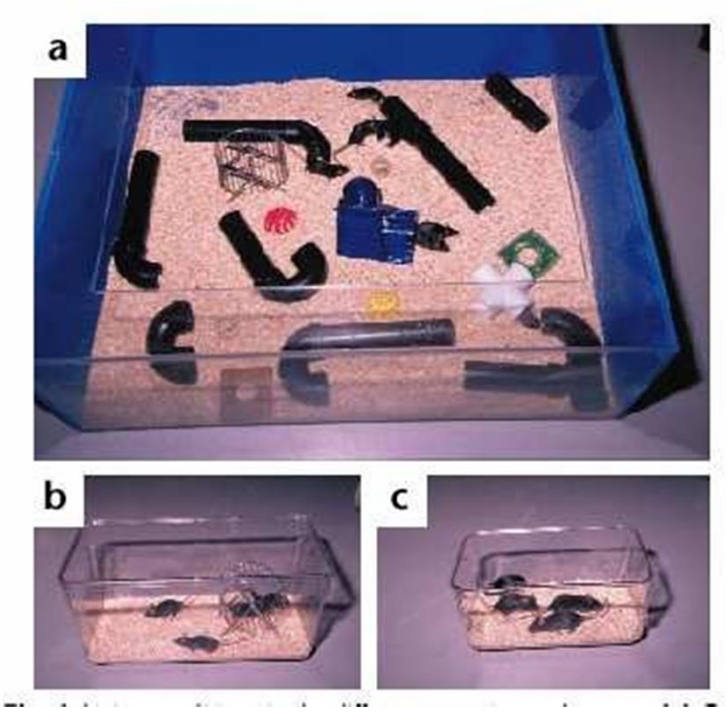
Modulation de la neurogénèse par lœenvironnement

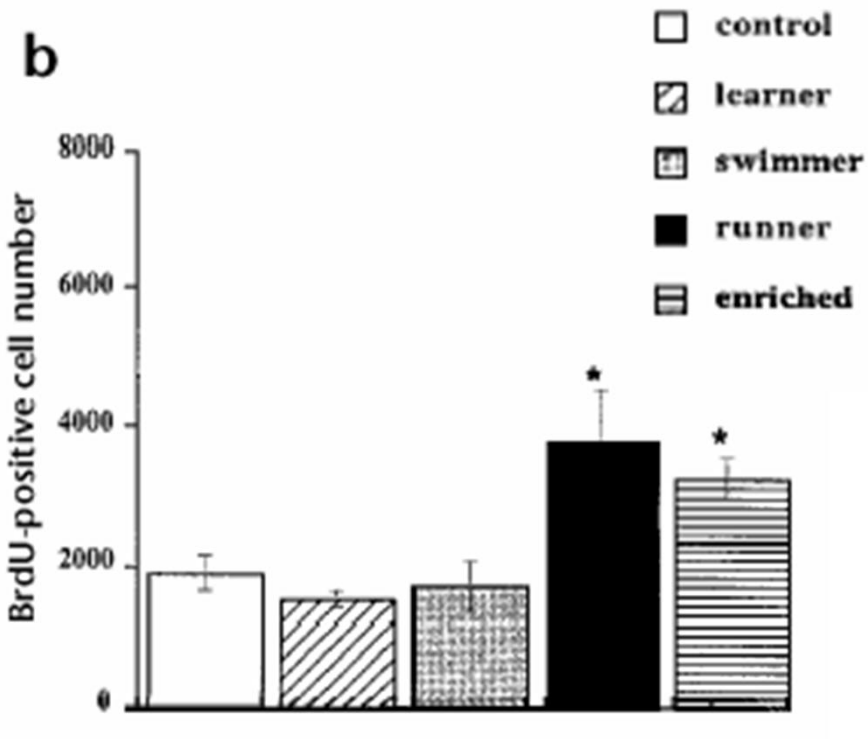
More hippocampal neurons in adult mice living in an enriched environment.

Nature. 1997 Apr 3;386(6624):493-5.

Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus.

Nat Neurosci. 1999 Mar;2(3):266-70.



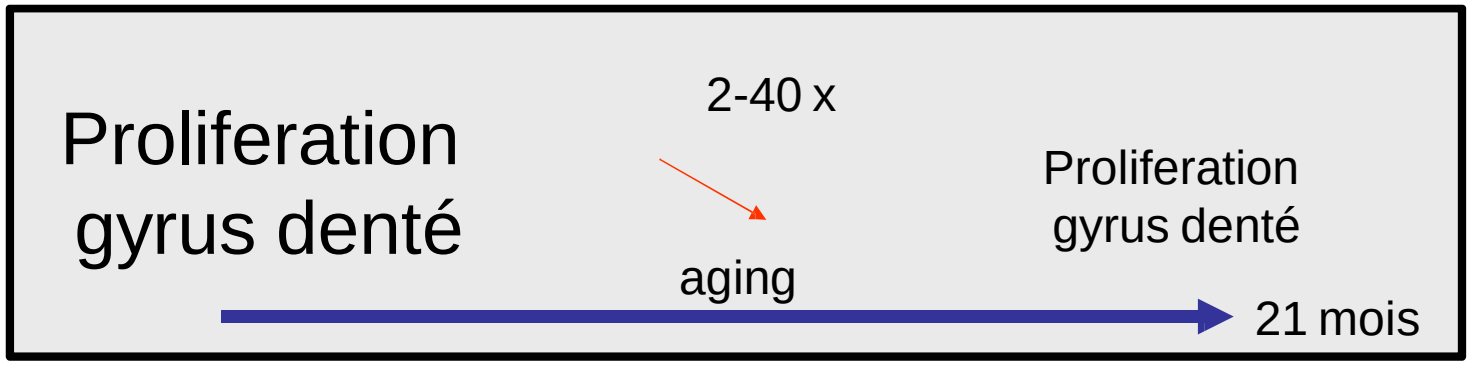


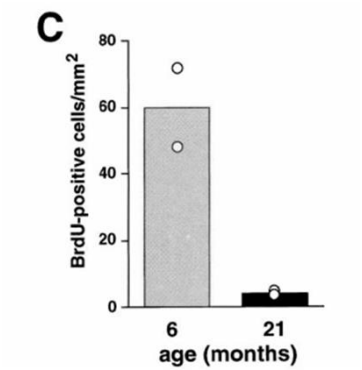
Facteurs affectant la neurogénèse de l'hippocampe chez les rongeurs

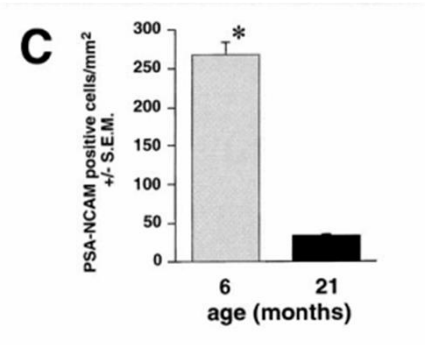
Exercice Physique	**Stress**
Environnement stimulant	**Dépression**
Facteurs de croissance (FGF, VEGF,é	**Régime alimentaire**
Glutamate (récepteur Kaïnaite)	**Glutamate (récepteur NMDA)**
Hormones (oestrogènes, prolactine,é)	**Morphine, Héroïne**
Dopamine, Sérotonine	**Alcool**
Antidépresseurs	**Privation de sommeil**
DHEA	**Age**

Effet du vieillissement sur la neurogénèse

Dans l'Hippocampe



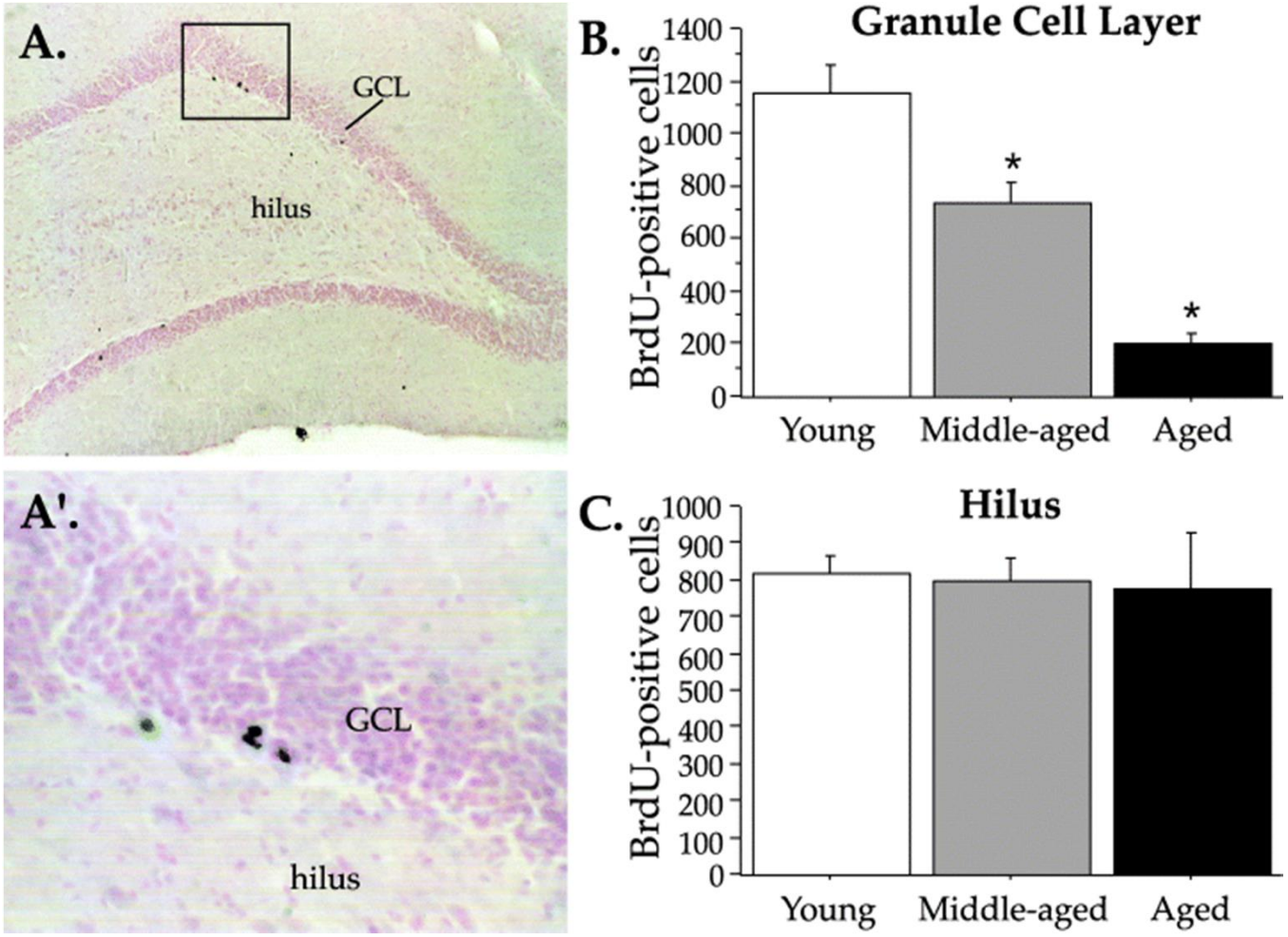




Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation.

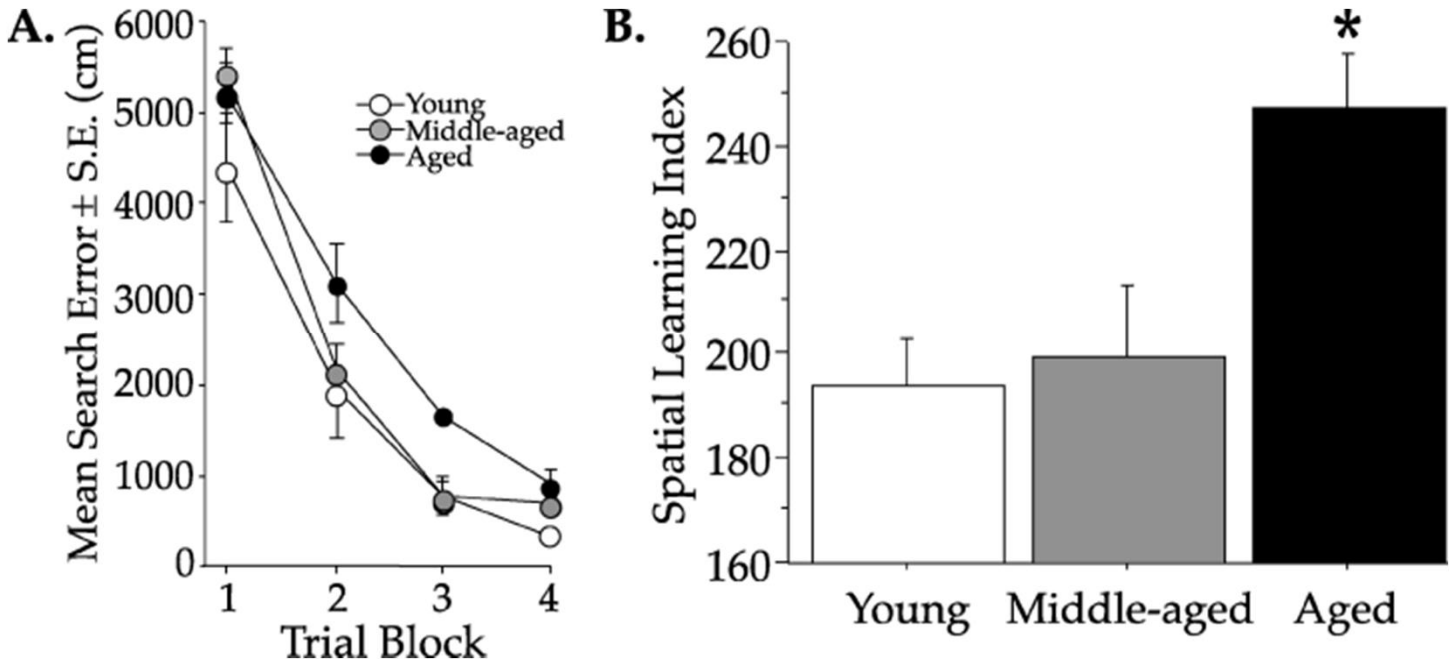
Kuhn HG, Dickinson-Anson H, Gage FH.
J Neurosci. 1996 Mar 15;16(6):2027-33.

Aging and Neurogenesis



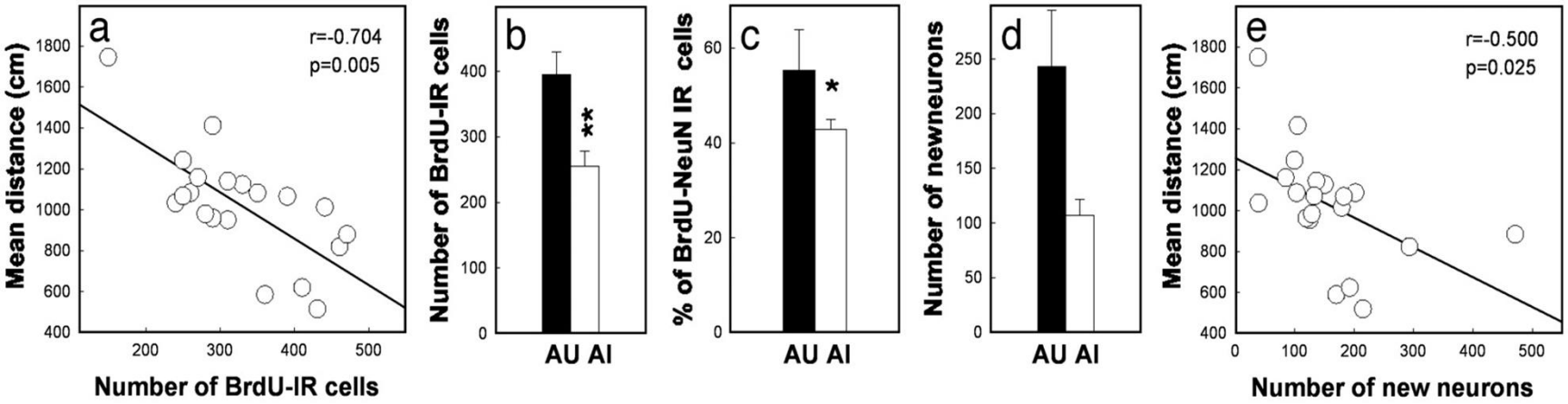
Bizon & Gallagher, *Eur J Neuroscience, 2003*

Aging, Neurogenesis and Water maze performance



Bizon & Gallagher, *Eur J Neuroscience, 2003*

Neurogenesis and Learning in Aged Rats



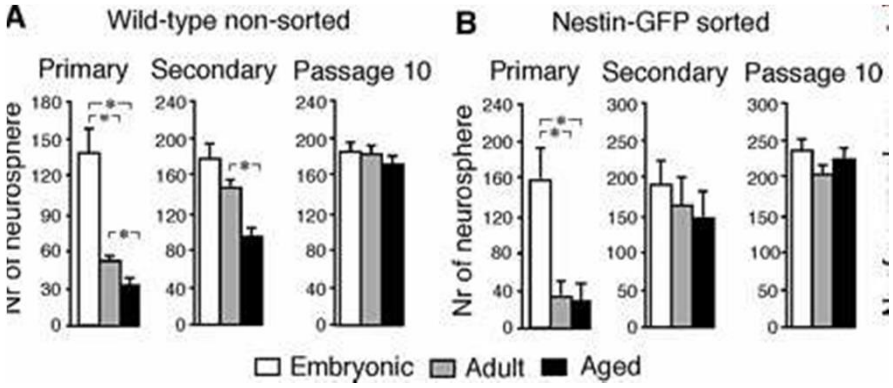
Survival and differentiation of newly generated cells in the granule cell layer. Performance on MWM (Morris water maze) as a function of new cells/neurons. Differences between upper 30% (Age Unimpairedò- AU) and lower 30% (ñAge Impairedò- AI) animals on cell counts.

Drapeau, et al., *Proc Nat Acad Sci*, 2003

Dans la zone sous ventriculaire

- Forte diminution de la prolifération, mais maintien ou faible réduction du nombre de cellules souches (J Neuro, 1997, 17 (20), 7850 + Maslov AY, J Neuroscience, 2004, 24(7) 1726)

- Forte diminution de la prolifération et baisse du nombre de cellules souches (90%) à 24 mois, (Blackmore, 2009, Stem cells, + Alhenius J Neuroscience, 2009, 29(14), 4408)



- **Conclusions convergentes sur la baisse de la prolifération mais divergentes sur le maintien ou non des cellules souches chez lôanimal âgé**

Les coupables

1-Quiescence + Sénescence

2-Cytokines, Cortisol

3-Modifications morphologiques de la niche

Cell Stem Cell
Article

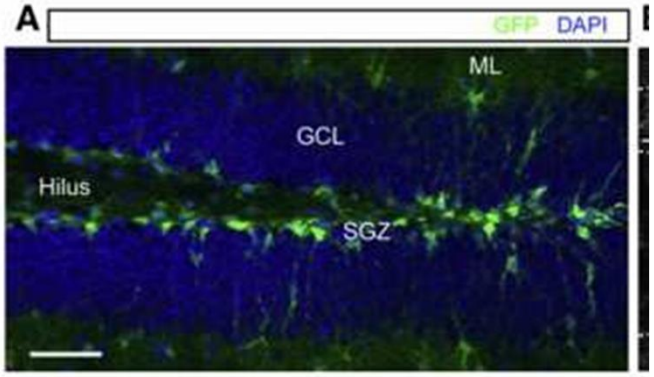
La Quiescence

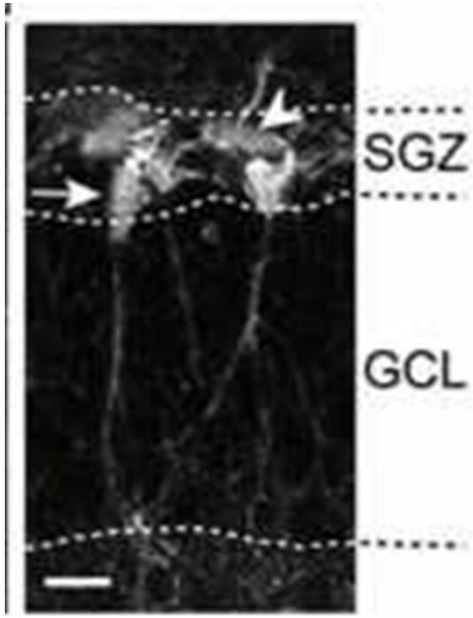
Quiescent and Active Hippocampal Neural Stem Cells with Distinct Morphologies Respond Selectively to Physiological and Pathological Stimuli and Aging

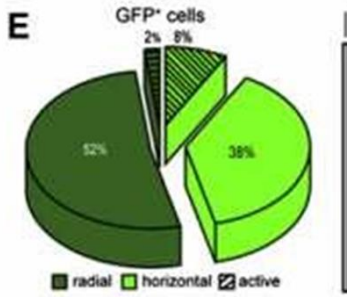
Sebastian Lugert,[1] Onur Basak,[1] Philip Knuckles,[1] Ute Haussler,[2] Klaus Fabel,[3] Magdalena Götz,[4,5] Carola A. Haas,[2] Gerd Kempermann,[3] Verdon Taylor,[1,6,7,*] and Claudio Giachino[1,7]

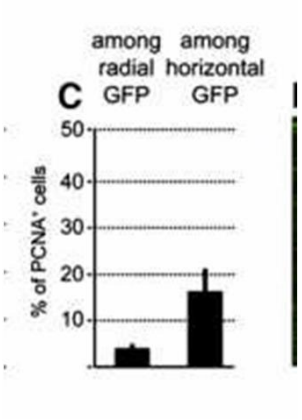
HES5-GFP mice (readout voie Notch)

2 types of stem cells



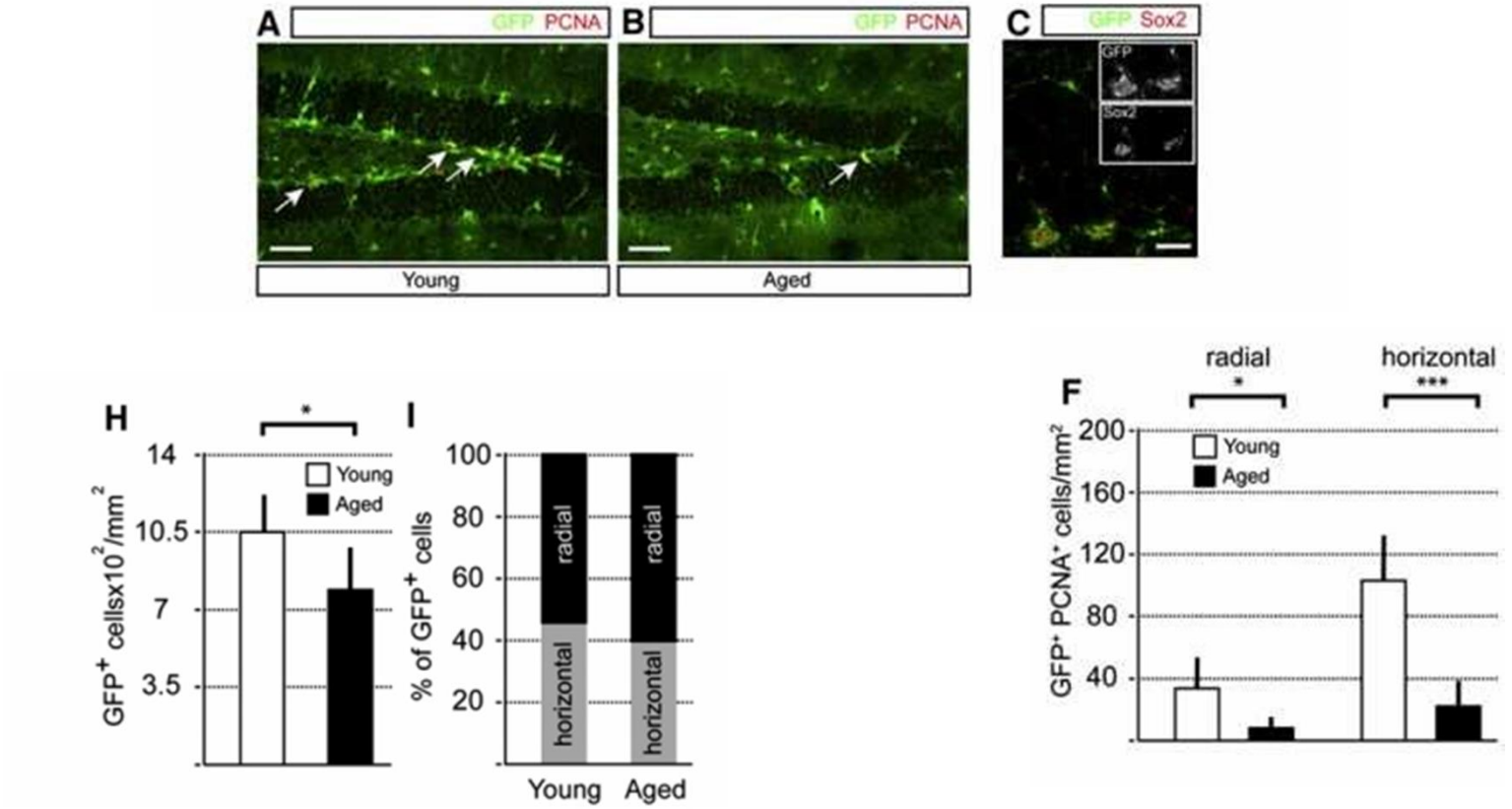






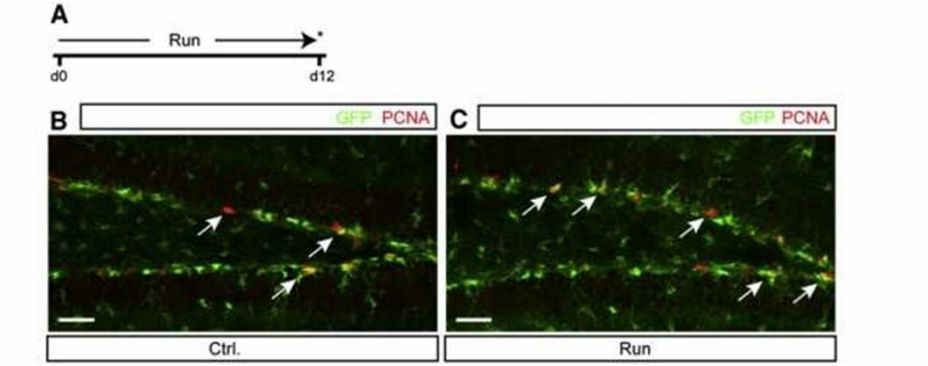
Les cellules souches horizontales sont les plus actives

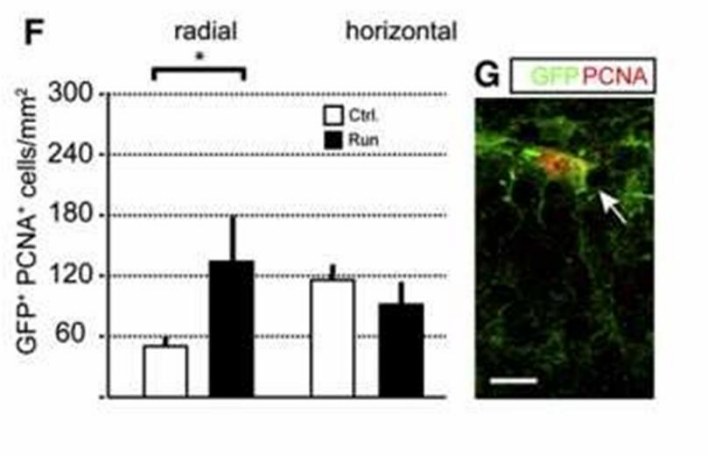
Figure 5. Loss of Horizontal Active NSCs during Aging



Pas de changement du nombre de cellules souches au cours du vieillissement mais baisse de la prolifération des cellules horizontales

L'exercice fait rentrer les cellules souches quiescentes radiales en prolifération





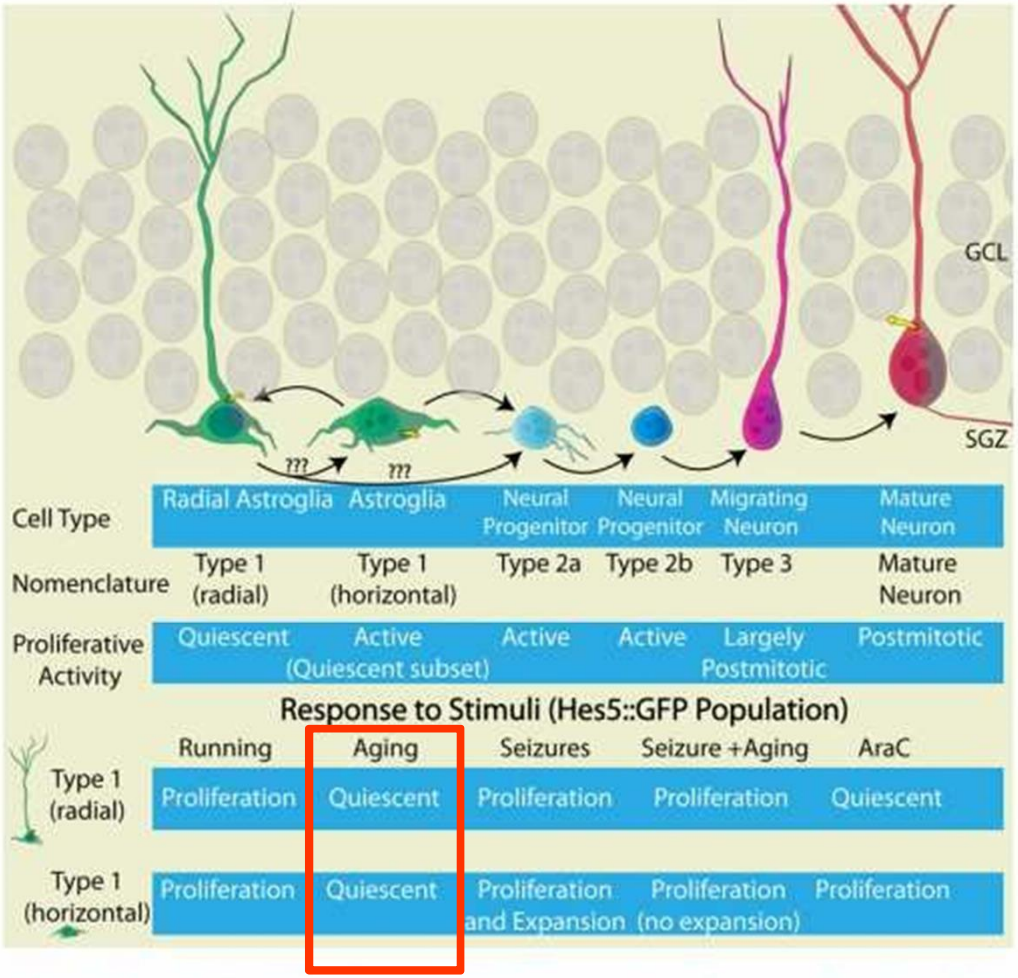


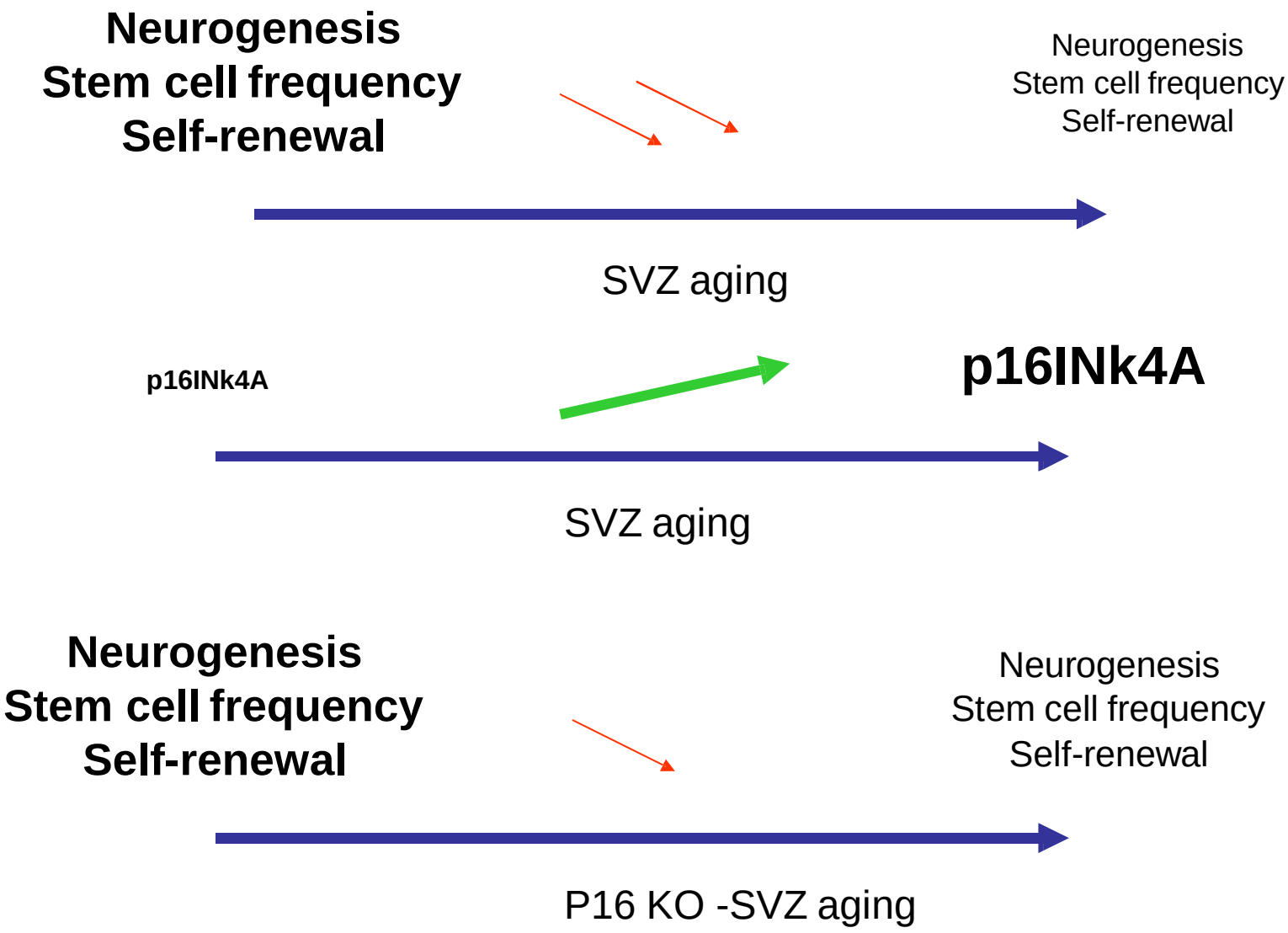
Figure 1. Current View of the Sequence of Neurogenesis from Precursor/Progenitor Cells in the Adult Dentate Gyrus

GFAP$^+$ Type 1 neural stem/precursor cells are believed to divide asymmetrically to give rise to more committed daughter cell types. However, some doubt exists as to the precise lineage relationships between radial and horizontal Type 1 cells. Type 2a cells express Sox2 and Ascl1 but not GFAP$^+$. Type 2b cells begin to express mature neuronal markers such as Dcx. These cell types are believed to undergo symmetric neurogenic divisions. Type 3 cells are migrating neurons that will integrate into the granule cell layer over the course of several weeks in the rodent. Lugert et al. use a surrogate marker of Notch signaling (Hes5::GFP) to label Type 1 cells and show that running, aging, and seizure activity have varied effects on proliferation and expansion of radial and horizontal progenitor populations.

Breunig, Cell Stem cells2010

La Sénescence

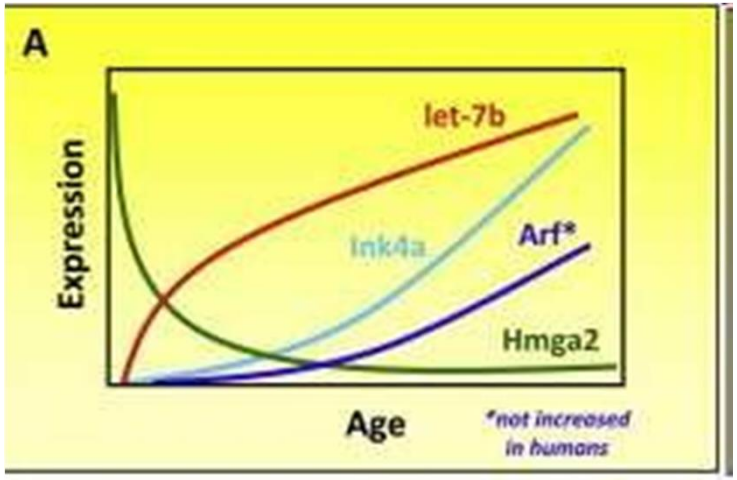
Nature. 2006 Sep 28;443(7110):448-52. Epub 2006 Sep 6.
Increasing p16INK4a expression decreases forebrain progenitors and neurogenesis during ageing.

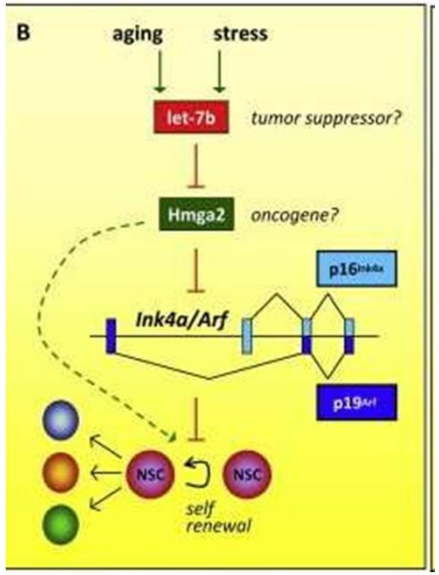


Ink4a/Arf regulation by let-7b and Hmga2: a genetic pathway governing stem cell aging.

Tzatsos A, Bardeesy N.

Cell Stem Cell. 2008 Nov 6;3(5):469-70.



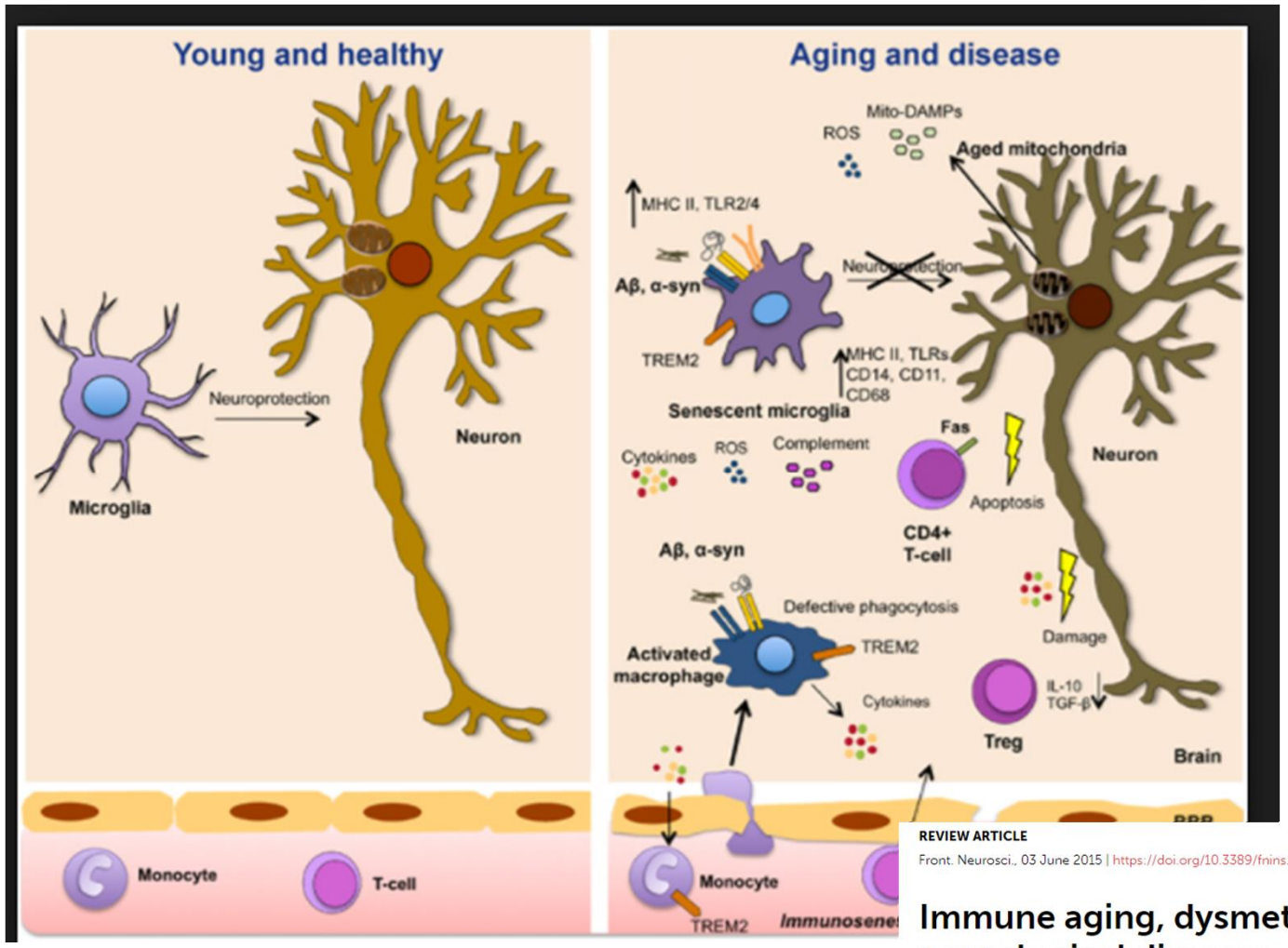


Let7b ⊣ Hmga2 ⊣ P16(Ink4a) P19 (Arf) → senescence

Qui fait augmenter Let7b ??

Les cytokines
Vieillissement cérébrale et Inflammation

Age-related cognitive decline is due in part to age-related increases in inflammation



REVIEW ARTICLE

Front. Neurosci., 03 June 2015 | https://doi.org/10.3389/fnins.2015.00172

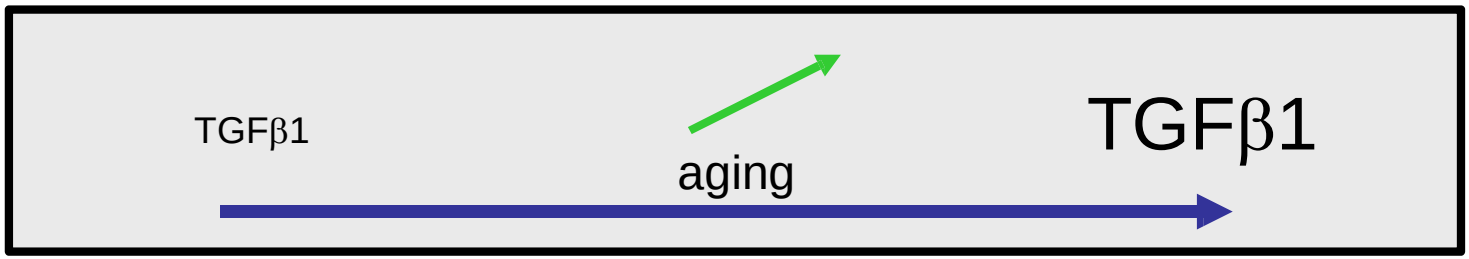
Immune aging, dysmetabolism, and inflammation in neurological diseases

Michela Deleidi[1]*, Madeline Jäggle[1] and Graziella Rubino[2]

Les cytokines

Un rôle du TGF b1 ??

Buckwalter, 2006, Am J Pathol



Experiment: TGFβ1 overexpression in Astrocytes

Result: blockade of hippocampic neurogenesis even in young animals

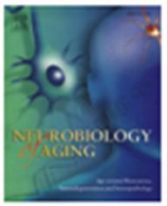
Influence of BMP proteins on neurogenesis declines

Neurobiology of Aging 38 (2016) 164–175

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging



Increased bone morphogenetic protein signaling contributes to age-related declines in neurogenesis and cognition

Emily A. Meyers*, Kevin T. Gobeske, Allison M. Bond, Jennifer C. Jarrett, Chian-Yu Peng, John A. Kessler

Department of Neurology, Northwestern University's Feinberg School of Medicine, Chicago, IL, USA

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Aging
Dentate gyrus
Environmental enrichment
Neural stem cell
Novel object recognition

ABSTRACT

Aging is associated with decreased neurogenesis in the hippocampus and diminished hippocampus-dependent cognitive functions. Expression of bone morphogenetic protein 4 (BMP4) increases with age by more than 10-fold in the mouse dentate gyrus while levels of the BMP inhibitor, noggin, decrease. This results in a profound 30-fold increase in phosphorylated-SMAD1/5/8, the effector of canonical BMP signaling. Just as observed in mice, a profound increase in expression of BMP4 is observed in the dentate gyrus of humans with no known cognitive abnormalities. Inhibition of BMP signaling either by over-expression of noggin or transgenic manipulation not only increases neurogenesis in aging mice, but remarkably, is associated with a rescue of cognitive deficits to levels comparable to young mice. Additive benefits are observed when combining inhibition of BMP signaling and environmental enrichment. These findings indicate that increased BMP signaling contributes significantly to impairments in neurogenesis and to cognitive decline associated with aging, and identify this pathway as a potential druggable target for reversing age-related changes in cognition.

TGFβ lengthens the G1 phase of stem cells in aged mouse brain.

Daynac M, **Pineda** JR, Chicheportiche A, Gauthier LR, Morizur L, Boussin FD, Mouthon MA.

Stem Cells. 2014 Dec;32(12):3257-65. doi: 10.1002/stem.1815.

Vascular-derived TGF-β increases in the stem cell niche and perturbs neurogenesis during aging and following irradiation in the adult mouse brain.

Pineda JR, **Daynac** M, Chicheportiche A, Cebrian-Silla A, Sii Felice K, Garcia-Verdugo JM, Boussin FD, Mouthon MA.

EMBO Mol Med. 2013 Apr;5(4):548-62.

Autre cytokine:
Influence of Interferons on brain aging

Science. 2014 Oct 3;346(6205):89-93. doi: 10.1126/science.1252945. Epub 2014 Aug 21.

Aging. Aging-induced type I interferon response at the choroid plexus negatively affects brain function.

Baruch K[1], Deczkowska A[1], David E[2], Castellano JM[3], Miller O[1], Kertser A[1], Berkutzki T[1], Barnett-Itzhaki Z[2], Bezalel D[2], Wyss-Coray T[3], Amit I[4], Schwartz M[5].

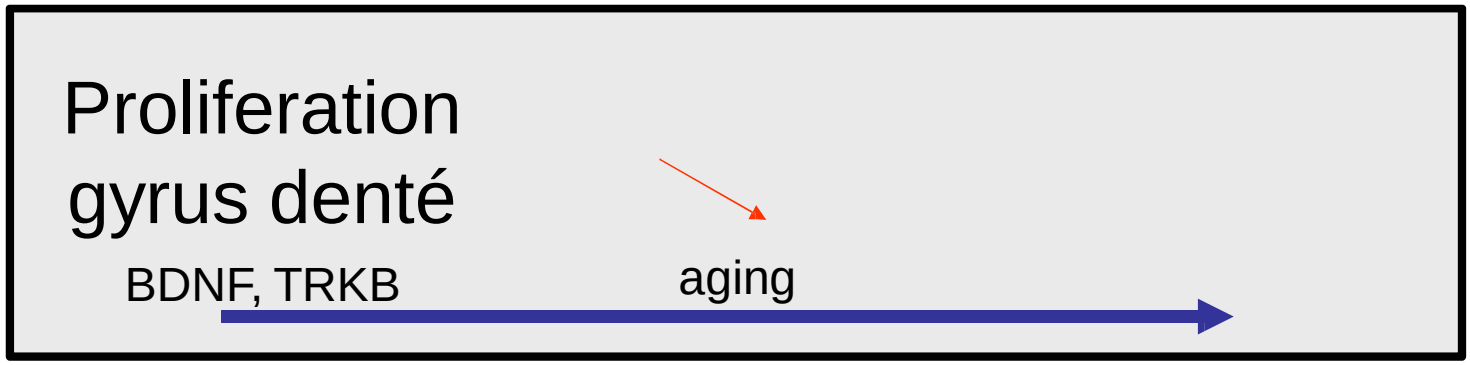
Author information

Abstract

Aging-associated cognitive decline is affected by factors produced inside and outside the brain. By using multiorgan genome-wide analysis of aged mice, we found that the choroid plexus, an interface between the brain and the circulation, shows a type I interferon (IFN-I)-dependent gene expression profile that was also found in aged human brains. In aged mice, this response was induced by brain-derived signals, present in the cerebrospinal fluid. Blocking IFN-I signaling within the aged brain partially restored cognitive function and hippocampal neurogenesis and reestablished IFN-II-dependent choroid plexus activity, which is lost in aging. Our data identify a chronic aging-induced IFN-I signature, often associated with antiviral response, at the brain's choroid plexus and demonstrate its negative influence on brain function, thereby suggesting a target for ameliorating cognitive decline in aging.

Mode dœaction de lœexercice

J Appl Physiol 2008, 105(5)



Proliferation
nombre de jeunes neurones,

5 week training

augmentation BDNF, TrkB,
Pas sur Corticosterone

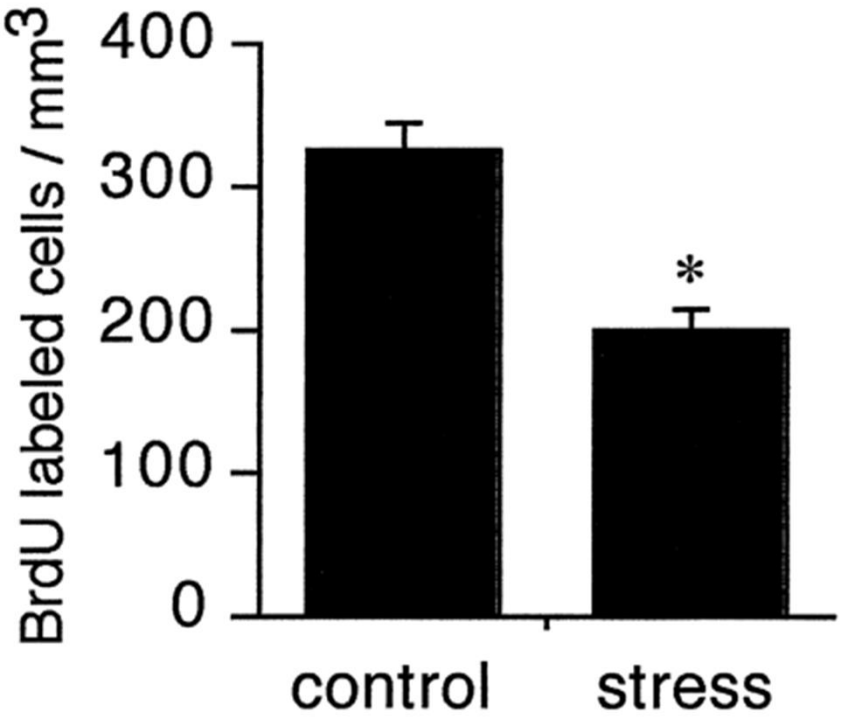
Mode dâaction de lâexercice

Exercise increases neural stem cell number in a growth hormone-dependent manner, augmenting the regenerative response in aged mice.
Blackmore DG, Golmohammadi MG, Large B, Waters MJ, Rietze RL.
Stem Cells. 2009 Aug;27(8):2044-52.

Les souris KO pour GH nâaugmente plus la neurogénèse chez des souris KO pour GH

Effet du cortisol sur la Neurogénèse

Predator Stress and Neurogenesis



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.

Gould, et. al., *Proc Nat Acad Sci*, 1998

Adrenal Steroids Mediate Stress Effect on neurogenesis

- Adrenal steroid production lowest in early prenatal period ï neurogenesis highest; vice versa in older animals

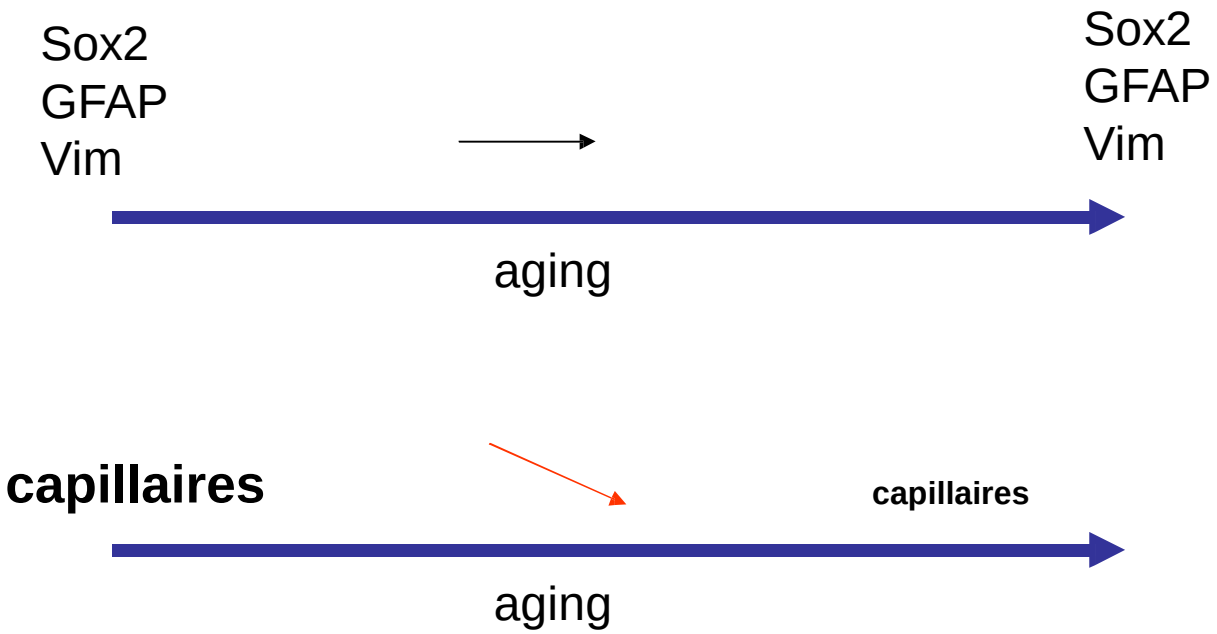
- Experimental increases in adrenal steroid produce reductions in neurogenesis

- Removal of adrenal steroids (adrenalectomy) associated with increase in neurogenesis

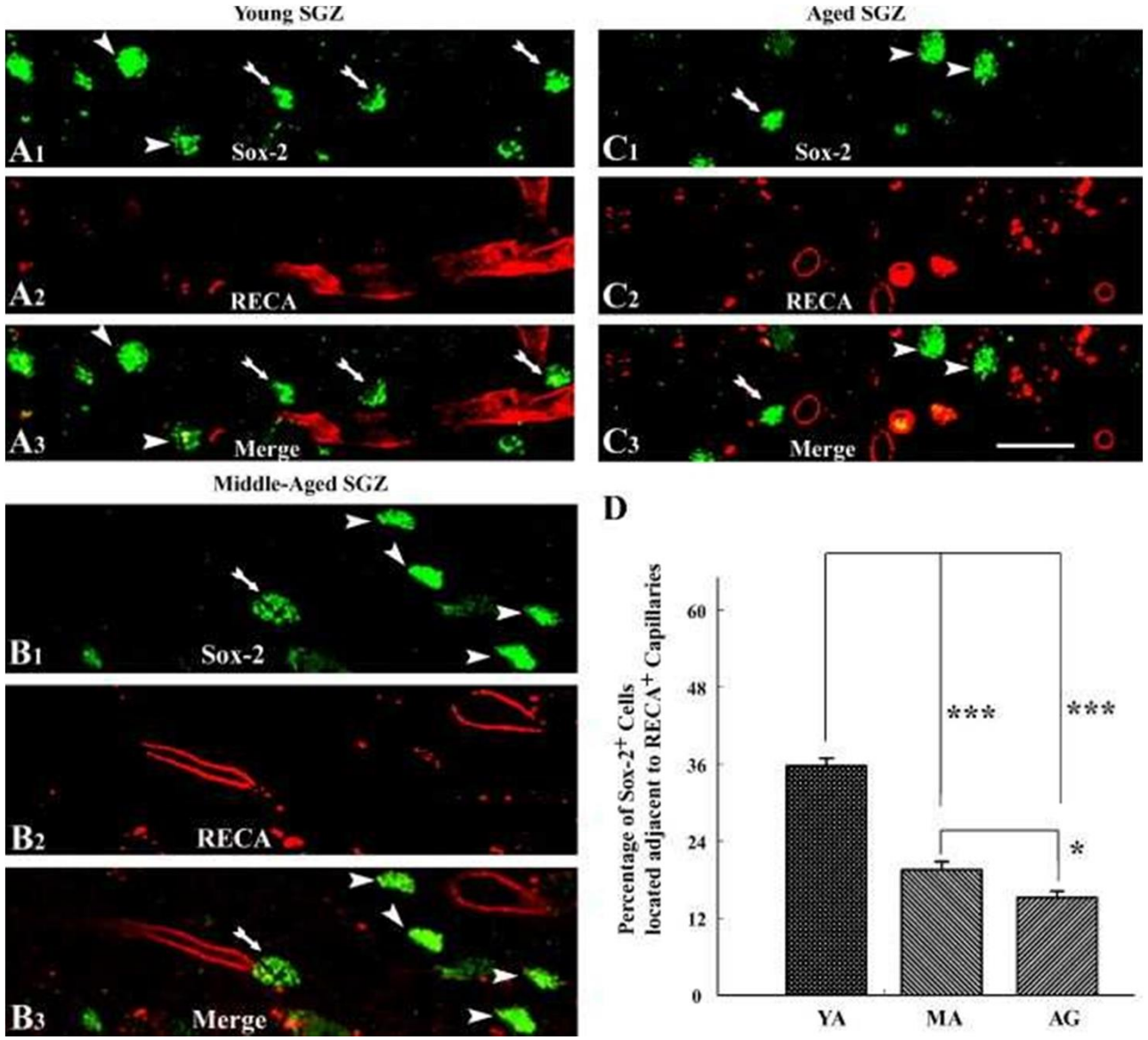
Modification morphologique de la niche au cours du vieillissement

Un effet sur la niche vasculaire

Hattiangady, Neurobiol Aging, 2008



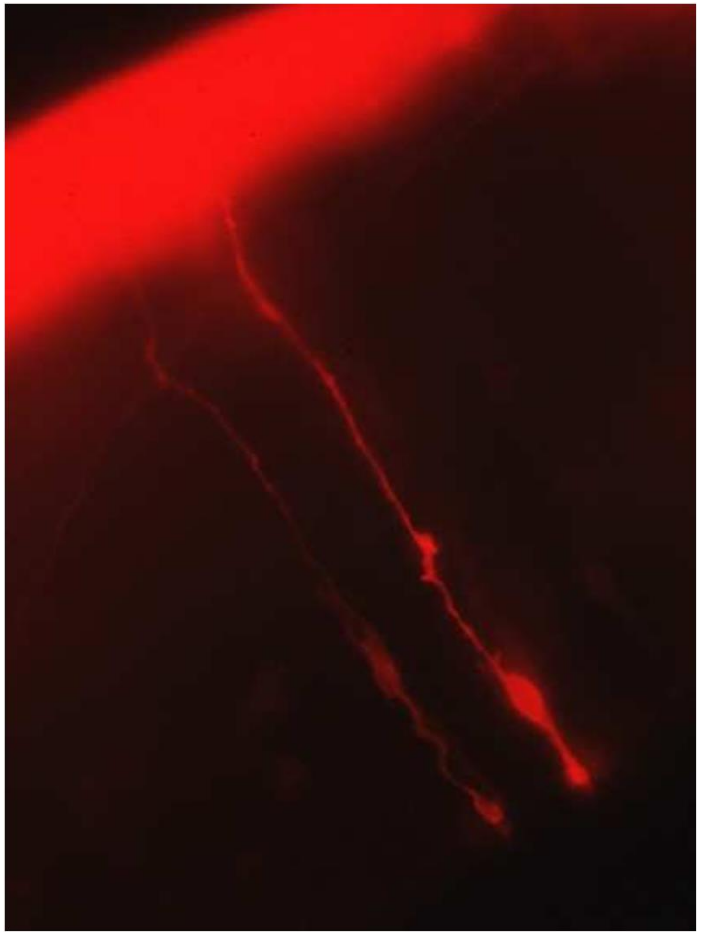
Les cellules Sox2+ sont plus loin des vaisseaux chez les animaux âgés



Vieillissement et centrosome

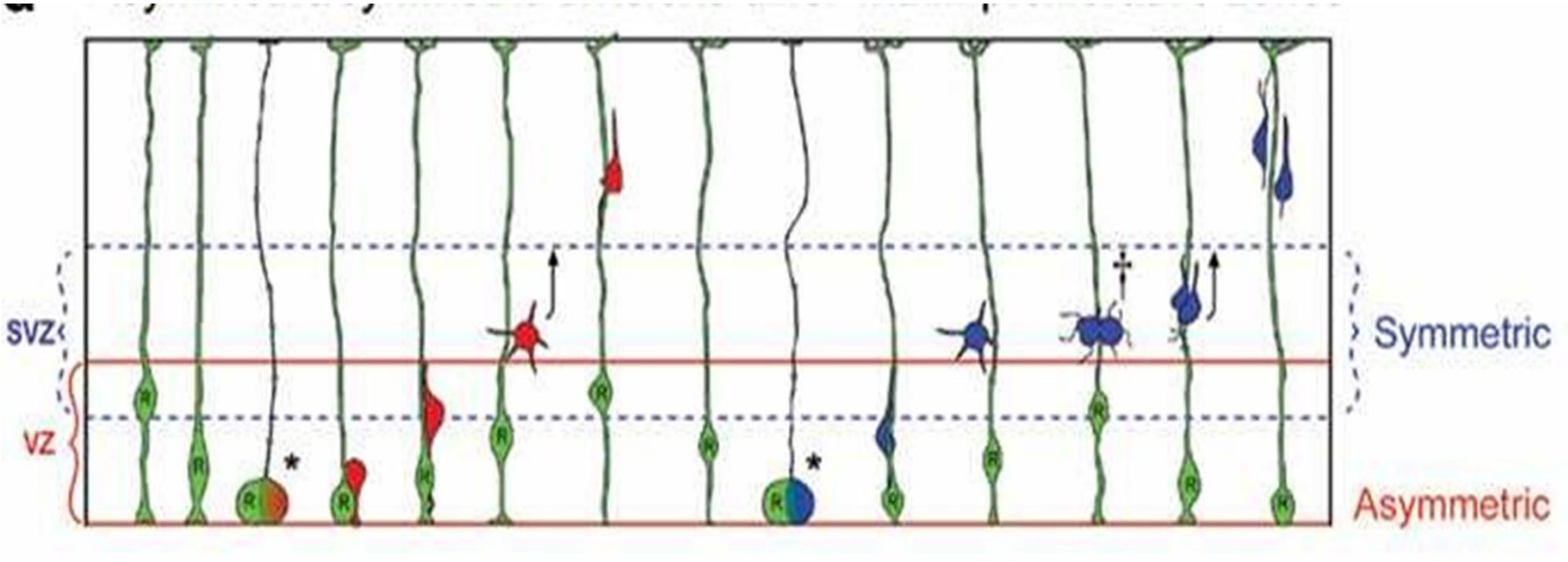
La glie radiaire forme les neurones par division asymétrique au cours du dvp du cerveau

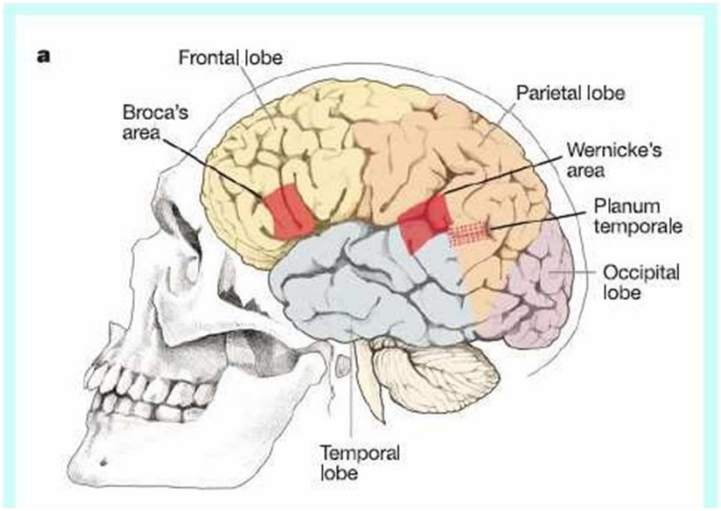
1973

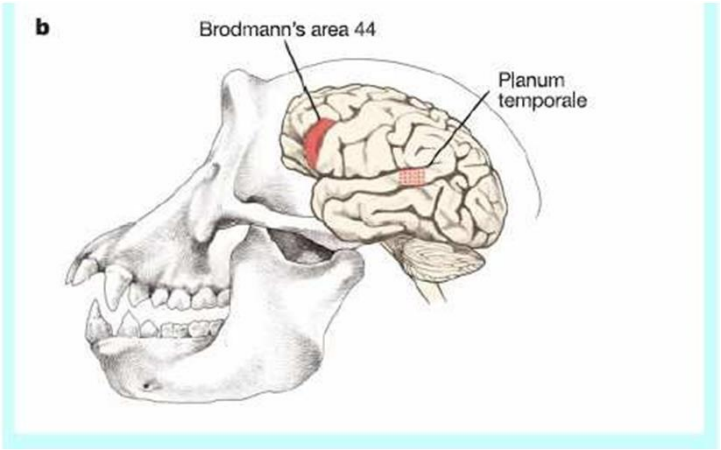


2000

Les cellules gliales radiales donnent soit directement des neurones (en rouge) soit des progéniteurs de neurones (en bleu) par division asymétrique





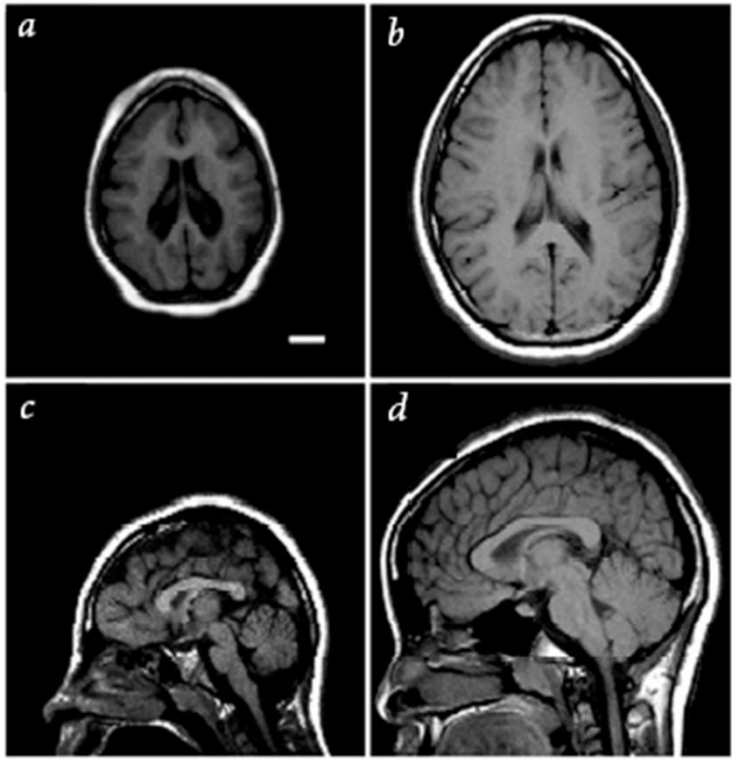


Microcéphalie: 3 gènes mutés codant pour des protéine du centrosome

Microcephaly (MCPH)

- Small (~430 cc v ~1,400 cc) but otherwise ~normal brain, only mild mental retardation

- Due to loss of activity of the *ASMP* gene, une protéine impliquée dans la division symétrique/asymétrique des cellules souches

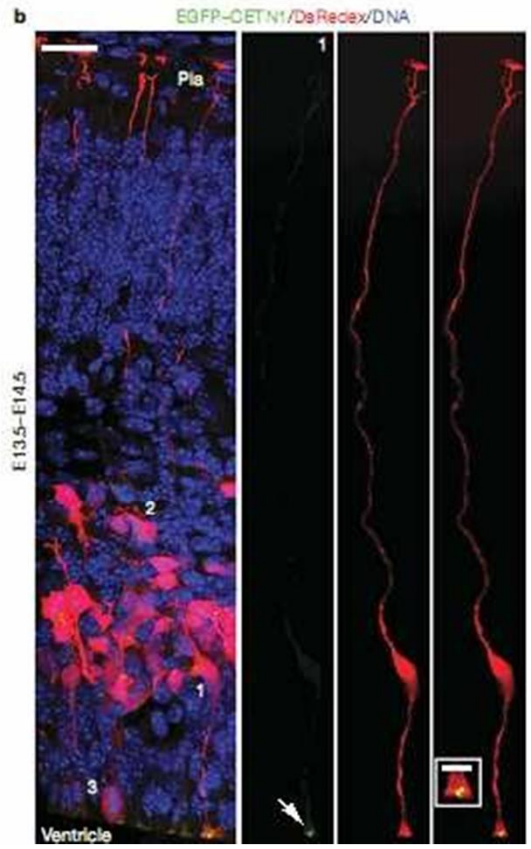


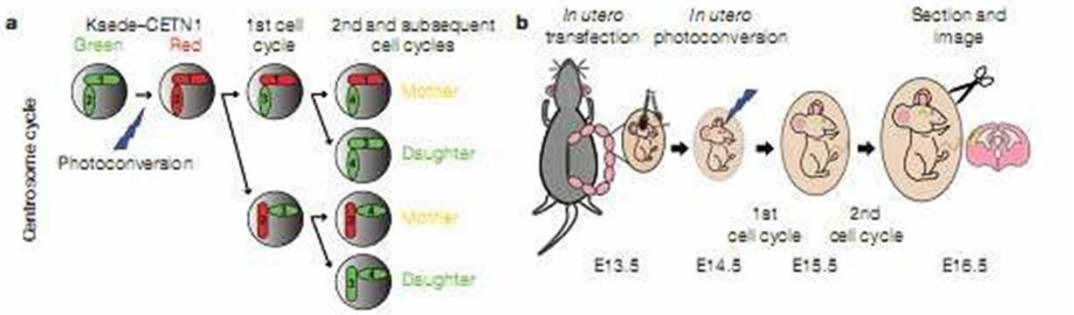
ASPM-/ASPM- control

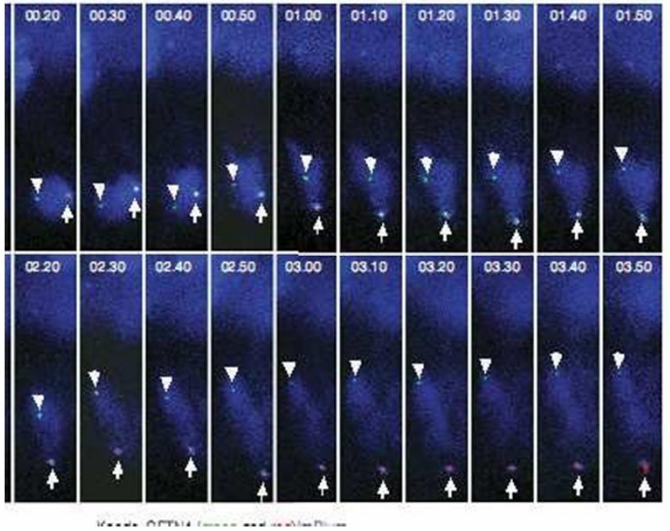
Bond *et al*. (2002) *Nature Genet*. **32**, 316-320

Asymmetric centrosome inheritance maintains neural progenitors in the neocortex

Xiaoqun Wang[1], Jin-Wu Tsai[2], Janice H. Imai[1,3], Wei-Nan Lian[2], Richard B. Vallee[2] & Song-Hai Shi[1,3]

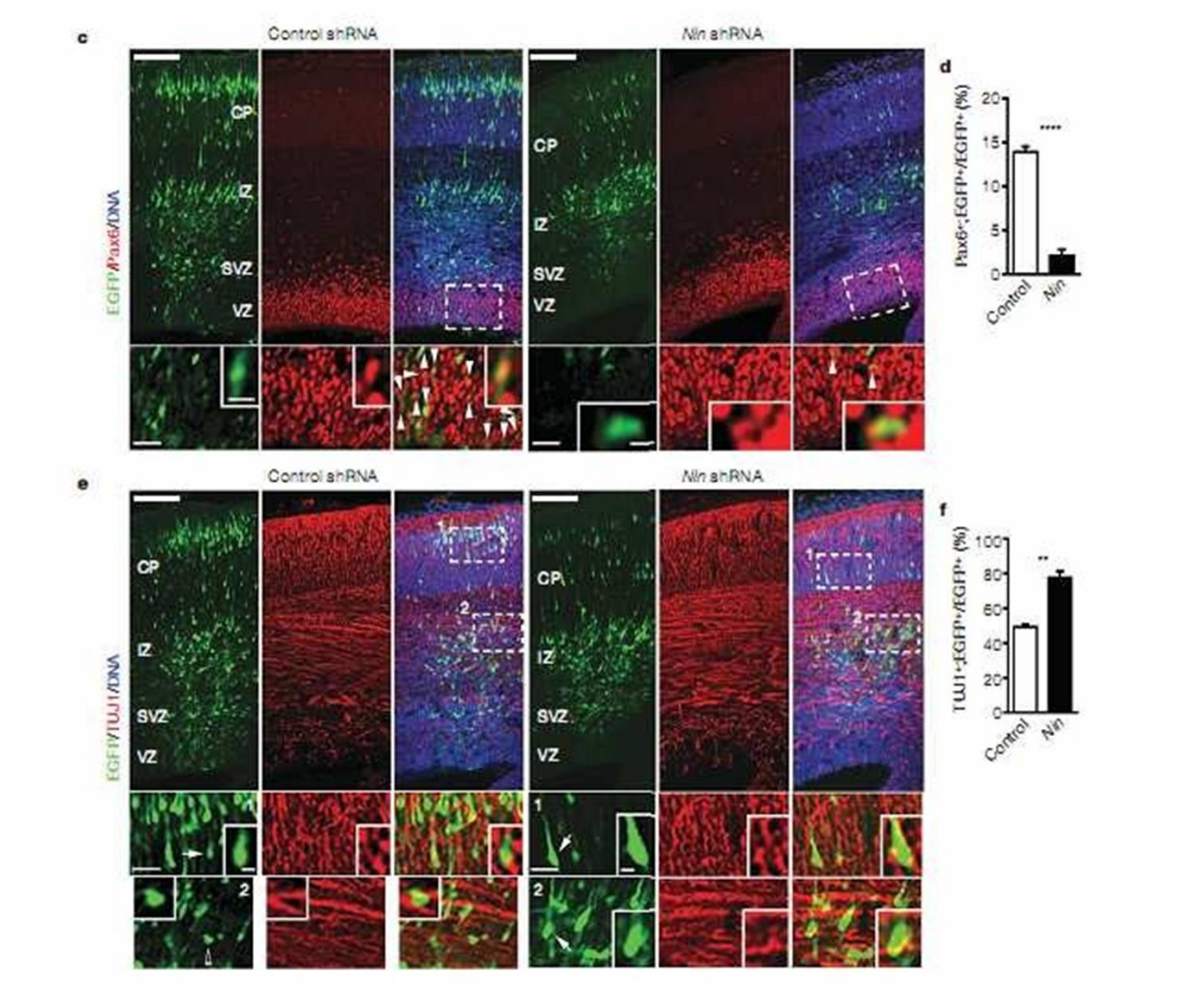






La cellule gliale radiale (stem cells) garde l'ancien centriole mère

L'inhibition de la ninein, une protéine du centrosome mature, provoque une diminution du nombre de cellules souches au profit de cellules différenciées



Centrosome misorientation reduces stem cell division during ageing

Jun Cheng[1]*, Nezaket Türkel[2]*†, Nahid Hemati[2]*, Margaret T. Fuller[4], Alan J. Hunt[1] & Yukiko M. Yamashita[2,3]

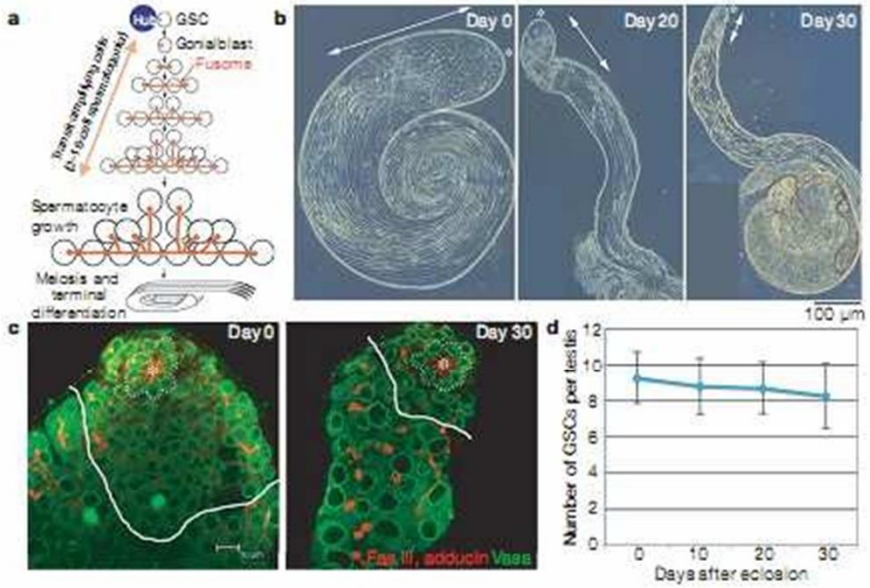


Figure 1 | *Drosophila* testis undergoes an age-related decline in spermatogenesis. **a**, Spermatogenesis of *Drosophila melanogaster* (adapted from ref. 27). GSCs are supported by the hub cells. Each spermatogonial division is incomplete, and the resultant spermatogonia and spermatocytes are connected by a cytoplasmic bridge, or a ring canal, through which a branched fusome runs. **b**, Phase microscopy of ageing testes. The apical (asterisk) area containing round, relatively early germ cells (arrow) decreases over time. **c**, The number of GSCs (surrounded by dotted line) remains constant with age. White lines separate spermatogonia and spermatocytes. Red, fasciclin III (Fas III; hub) and adducin (fusome); green, Vasa (germ cells). The hub is indicated by an asterisk. **d**, The number of GSCs is shown (±s.d.). $n > 50$ testes were counted for each time point.

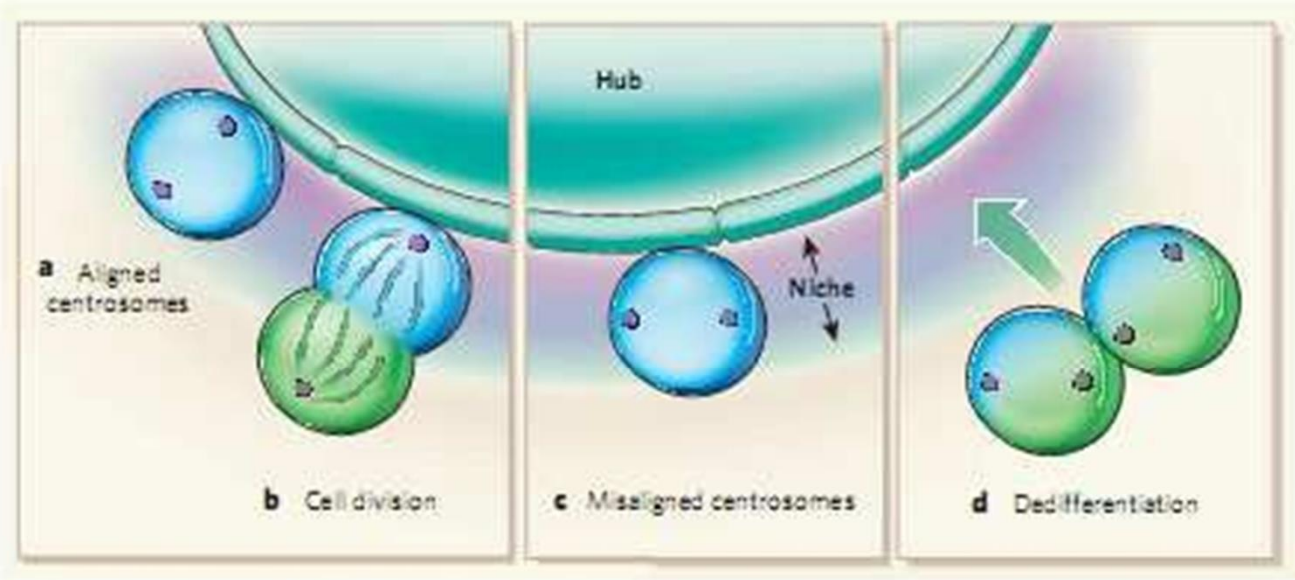


Figure 1 | Centrosome alignment and germline stem-cell (GSC) maintenance in the *Drosophila* testis niche[1]. **a**, Normally, GSCs keep one centrosome (purple circle) aligned with the support cells of the hub, so that upon division (**b**) one daughter will remain in the niche while the other will exit and differentiate. **c**, With increasing age, more and more GSCs have misaligned centrosomes — that is, neither is adjacent to the hub — and so do not divide. **d**, Some of these GSCs arise from dedifferentiating older germ cells that re-enter the niche with randomly positioned centrosomes.

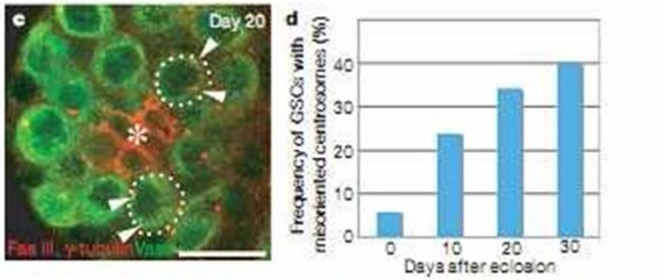


Figure 2 | Misoriented GSCs increase with age. **a**, Schematic diagram of

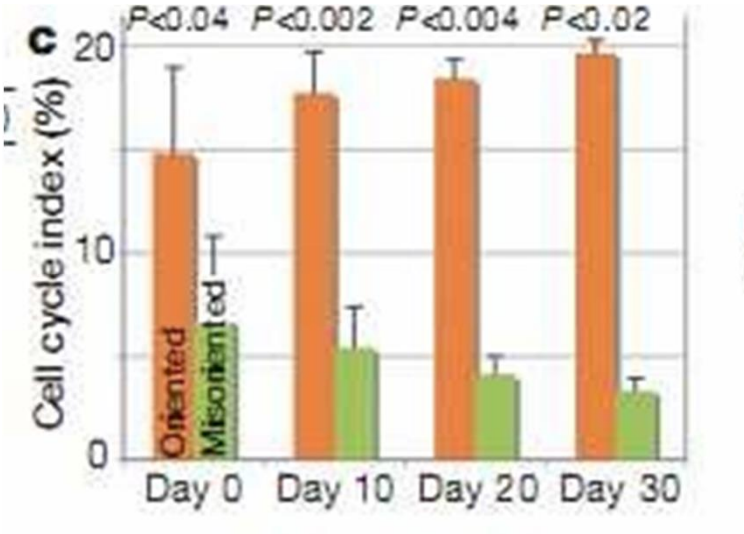
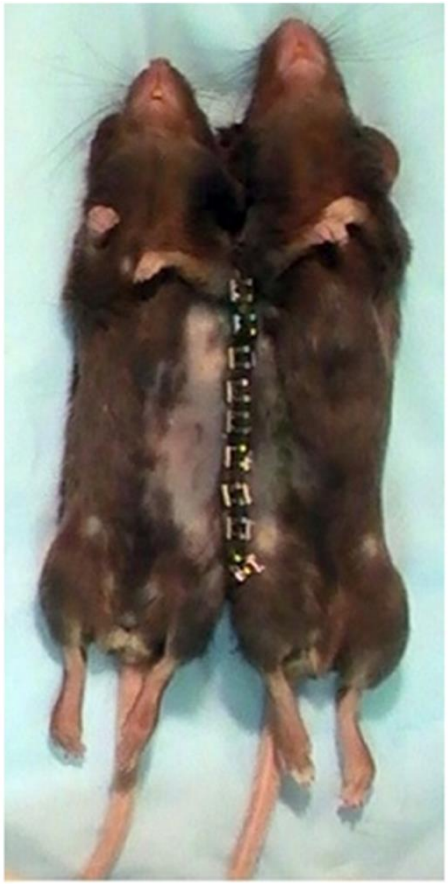
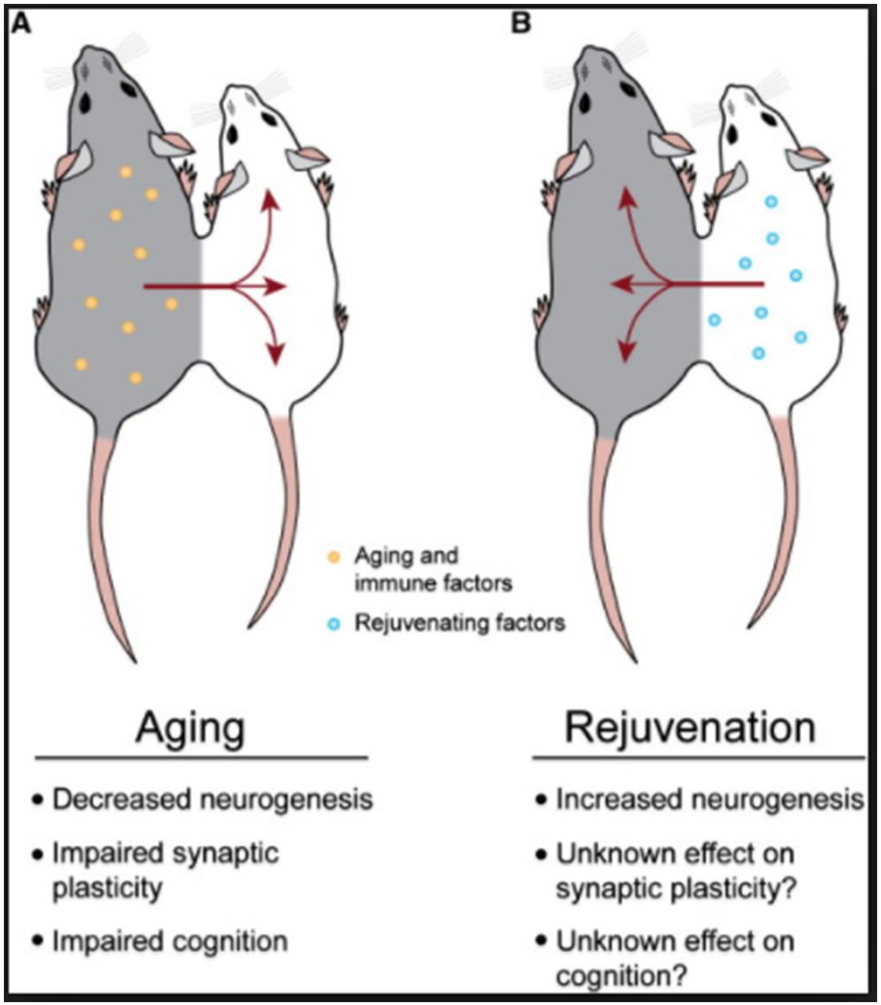


Figure 3 | Misoriented GSCs divide less frequently compared with oriented GSCs. **a**, Spindles remain oriented throughout mitosis even at day 30. Red,

REVUE POUR ALLER PLUS LOIN:

Rajeunir la niche de cellules souches
Expérience de parabiose





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INSTITUTE

USING YOUNG BLOOD TO REJUVENATE OLD HUMANS

GET INVOLVED

Young Blood Therapy | Plasma Replacement Therapy

We established the Young Blood Institute to advance new medical uses for well established blood plasma replacement immunotherapies that have recently evidenced previously undocumented potential to rejuvenate stems cells, restore aging

AMBROSIA

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YOUNG BLOOD TREATMENT

Science. 2014 May 9;344(6184):630-4. doi: 10.1126/science.1251141. Epub 2014 May 5.

Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors.

Katsimpardi L[1], Litterman NK, Schein PA, Miller CM, Loffredo FS, Wojtkiewicz GR, Chen JW, Lee RT, Wagers AJ, Rubin LL.

Author information

Abstract

In the adult central nervous system, the vasculature of the neurogenic niche regulates neural stem cell behavior by providing circulating and secreted factors. Age-related decline of neurogenesis and cognitive function is associated with reduced blood flow and decreased numbers of neural stem cells. Therefore, restoring the functionality of the niche should counteract some of the negative effects of aging. We show that factors found in young blood induce vascular remodeling, culminating in increased neurogenesis and improved olfactory discrimination in aging mice. Further, we show that GDF11 alone can improve the cerebral vasculature and enhance neurogenesis. The identification of factors that slow the age-dependent deterioration of the neurogenic niche in mice may constitute the basis for new methods of treating age-related neurodegenerative and neurovascular diseases.

Comment in

Brain ageing: Blood-derived rejuvenation. [Nat Rev Neurosci. 2014]

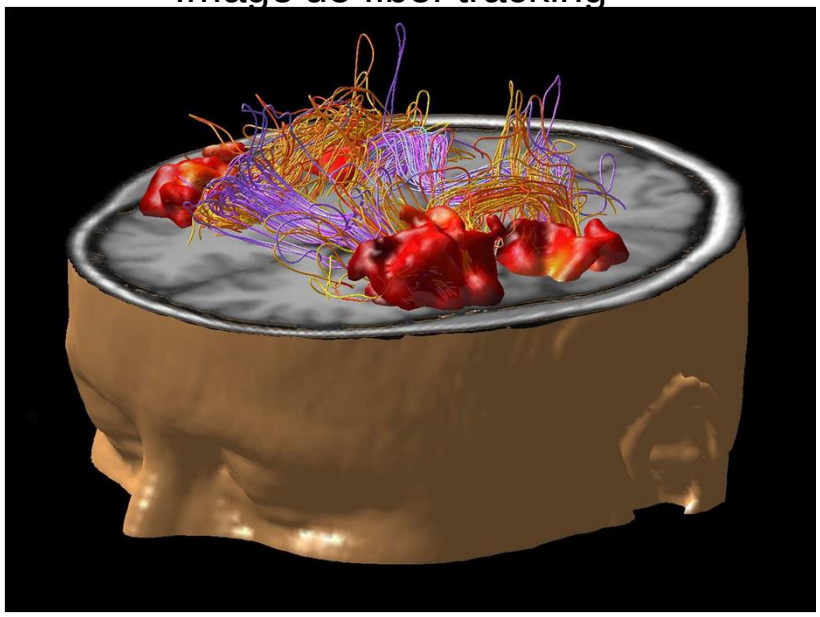
Young systemic factors as a medicine for age-related neurodegenerative diseases. [Neurogenesis (Austin). 2015]

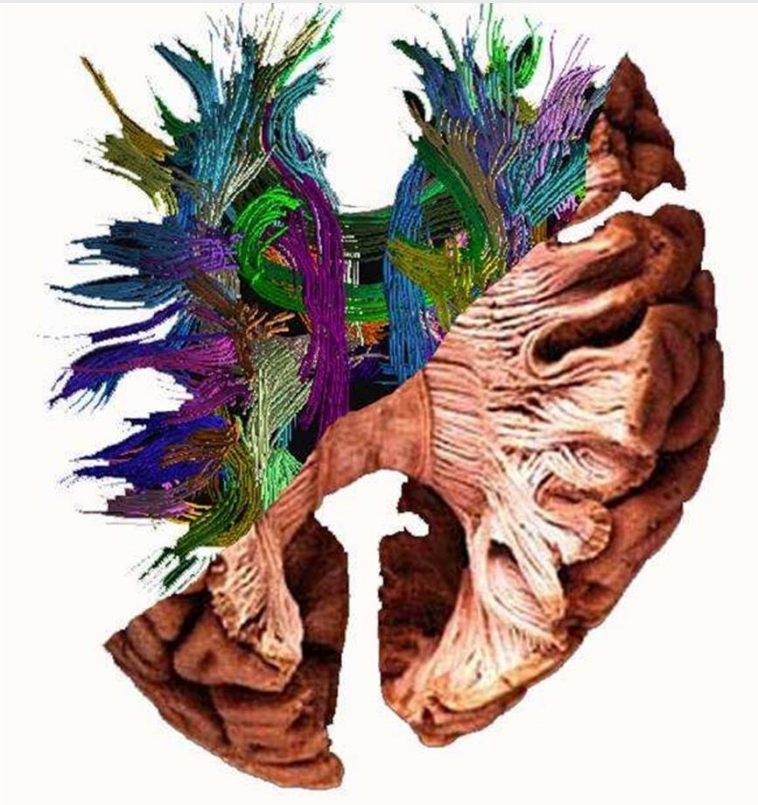
Ageing: Could young blood combat age-related cognitive decline? [Nat Rev Neurol. 2014]

Myélinisation, Remyelinisation et Vieillissement

Myelinisation

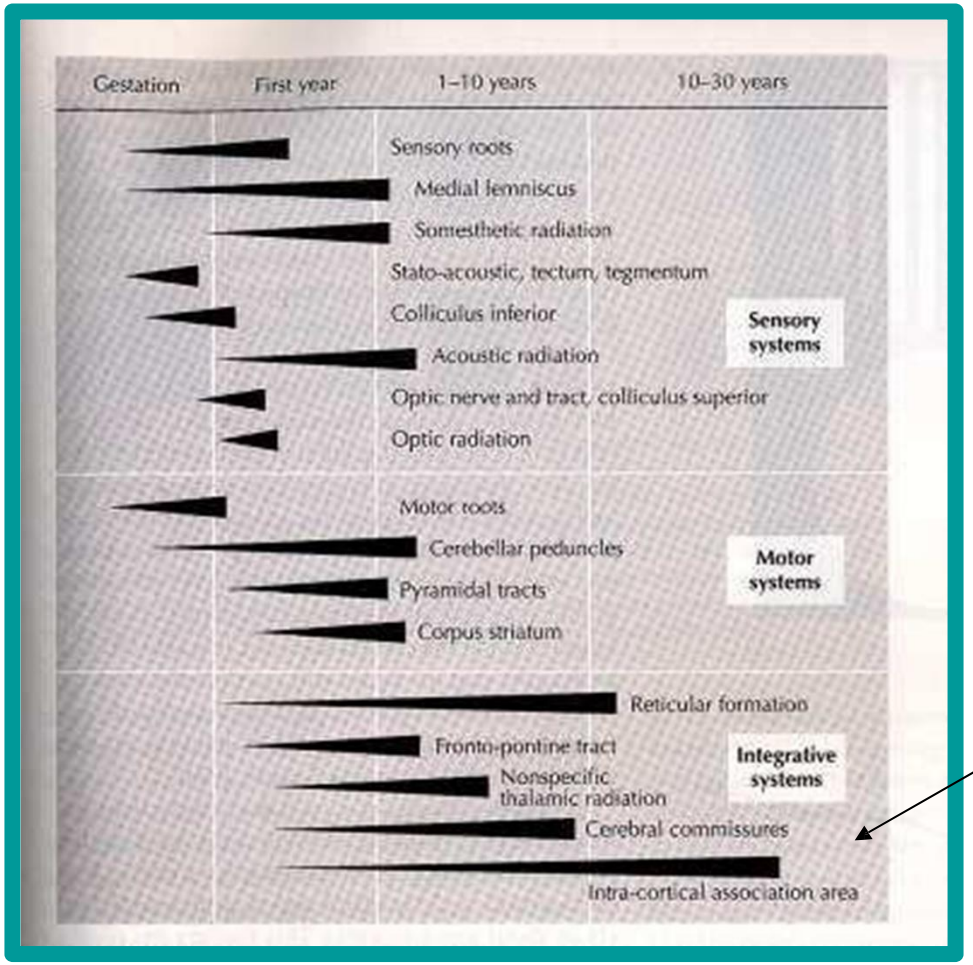
Image de fiber tracking





Un cerveau humain a 20 ans contient 176 000 km de fibres myélinisées (149 000 km chez la femme)

Myelinisation: essentiellement post natale



Myelinisation tardive des régions associatives

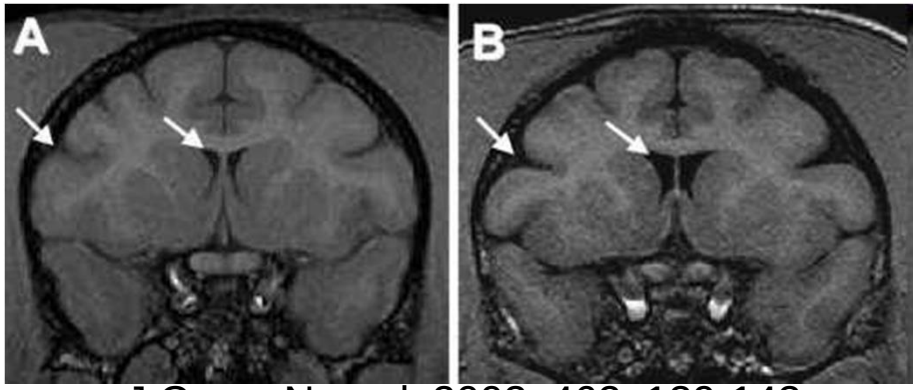
Substance Blanche et Vieillissement

- Lors du vieillissement du cerveau, la perte neuronale est faible (10%)

- Par contre la diminution de la substance blanche est importante: plus de 20% en volume associée à une perte du nombre de fibres myélinisées

Homme: 176 000 km à 20 ans, 97 200 à 80 ans: **45% de perte**

Singe de 7 ans Singe de 30 ans



J Comp Neurol, 2003, 462, 139-143

Figure 2. Representative T2-weighted scans from two rhesus monkeys taken at the level of the temporal pole. **A:** A young monkey (7 years old). **B:** An elderly monkey (30 years old). Note the enlargement of the ventricles and the sulci in B (arrows). Quantitative analysis of segmented images from young and old monkeys indicates that this gyral atrophy results from a decrease in white matter volume with a compensatory increase in ventricular volume.