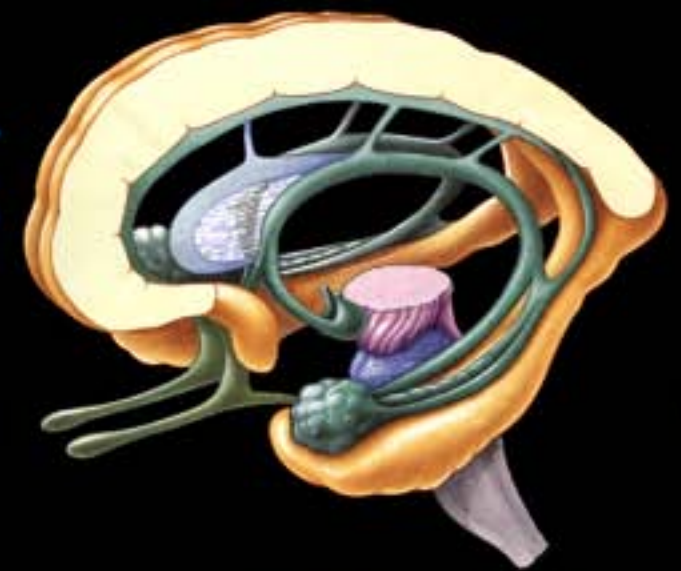


Hippocampal development & Synaptogenesis



Lydia Danglot

Module « Cellular Neurobiology & Development »

Magistère Européen de Génétique

UFR Sciences du Vivant - Université Denis Diderot Paris VII

22 septembre 2008



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Hippocampal development & Synaptogenesis

1. Introduction to neuroanatomy

Neurulation

Differentiation : Forebrain-Midbrain-Hindbrain

Major structures of the brain

2. Hippocampus & the limbic system

Localization in human and rodents

General function

Connections and cellular populations

3. Formation of the hippocampus and dentate gyrus

Migration of excitatory neurons

pyramidal cells & granule cells

Migration of inhibitory interneurons

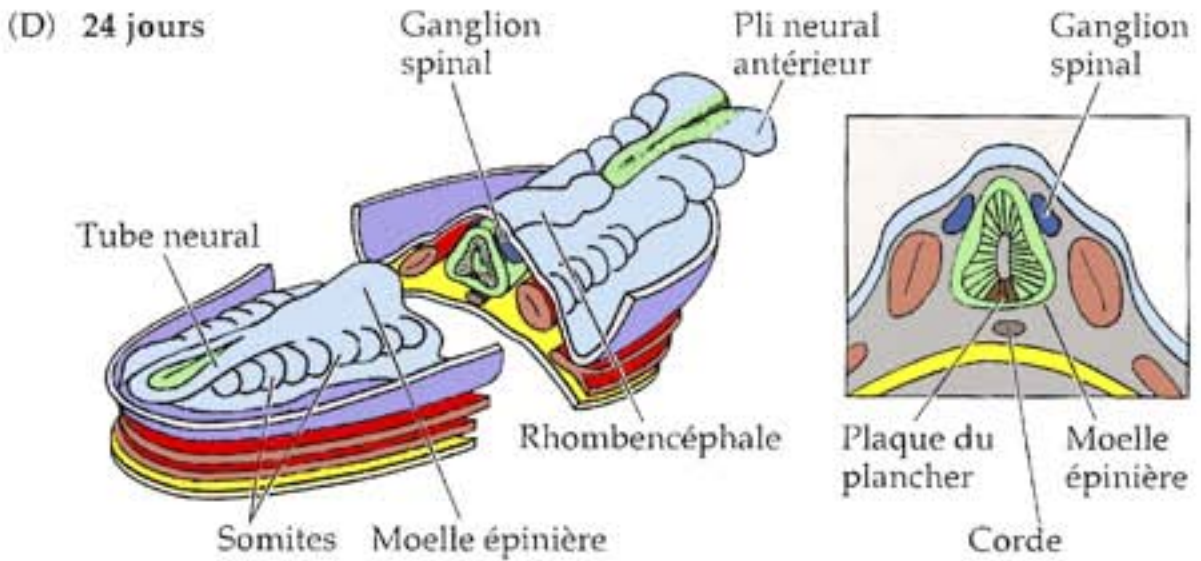
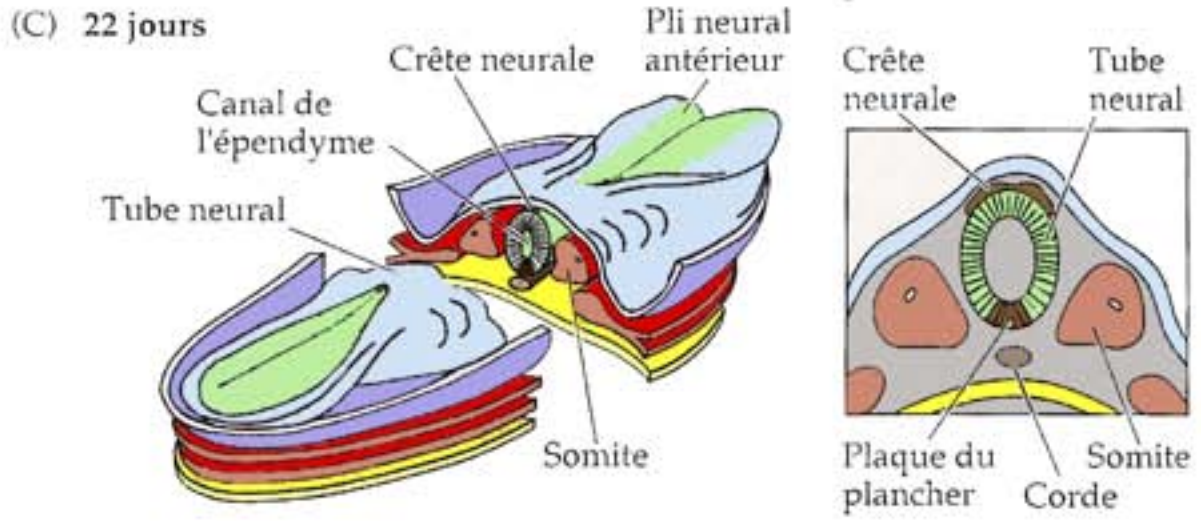
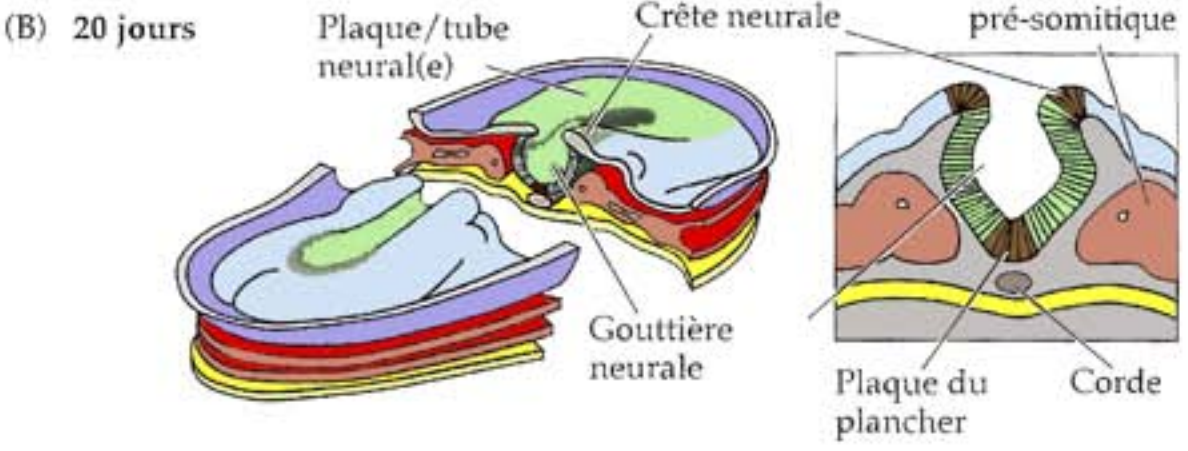
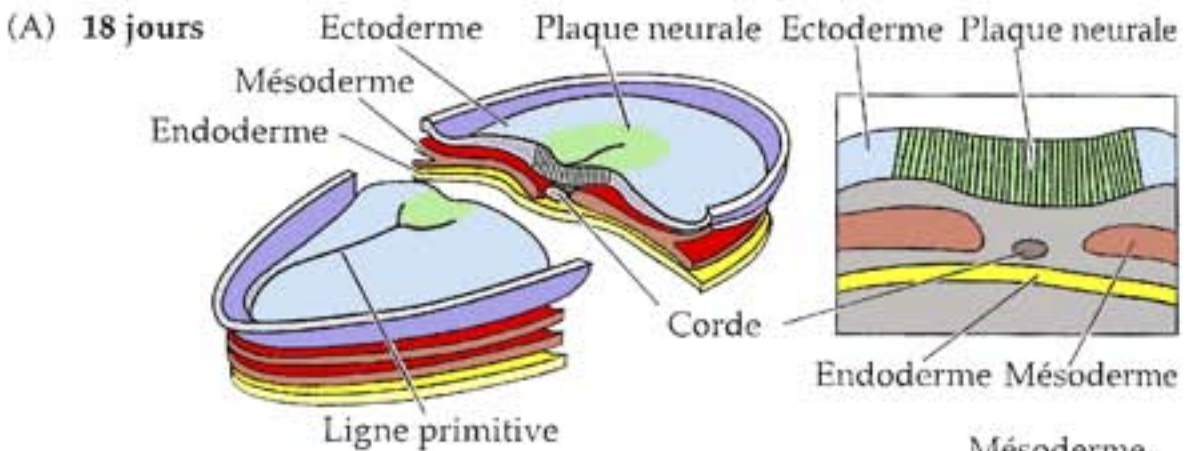
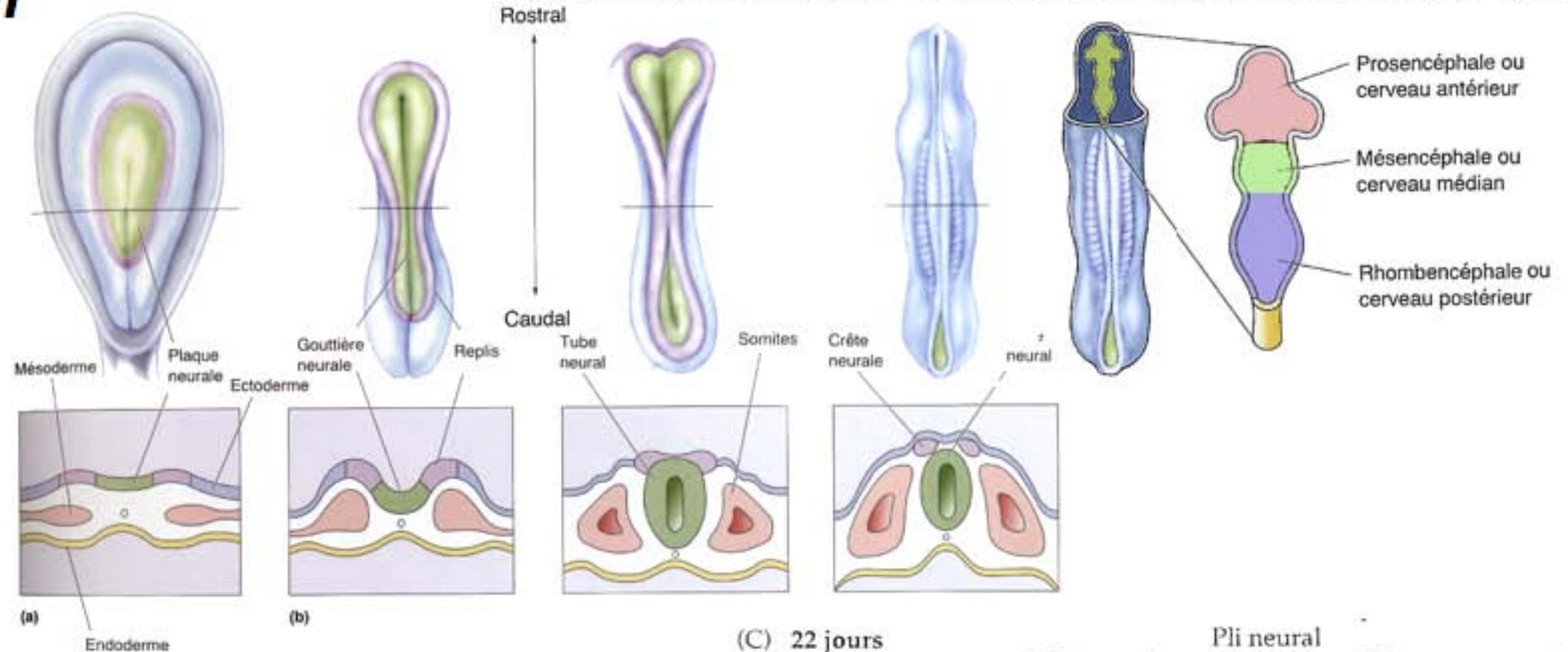
4. Dissociated hippocampal neurons in culture

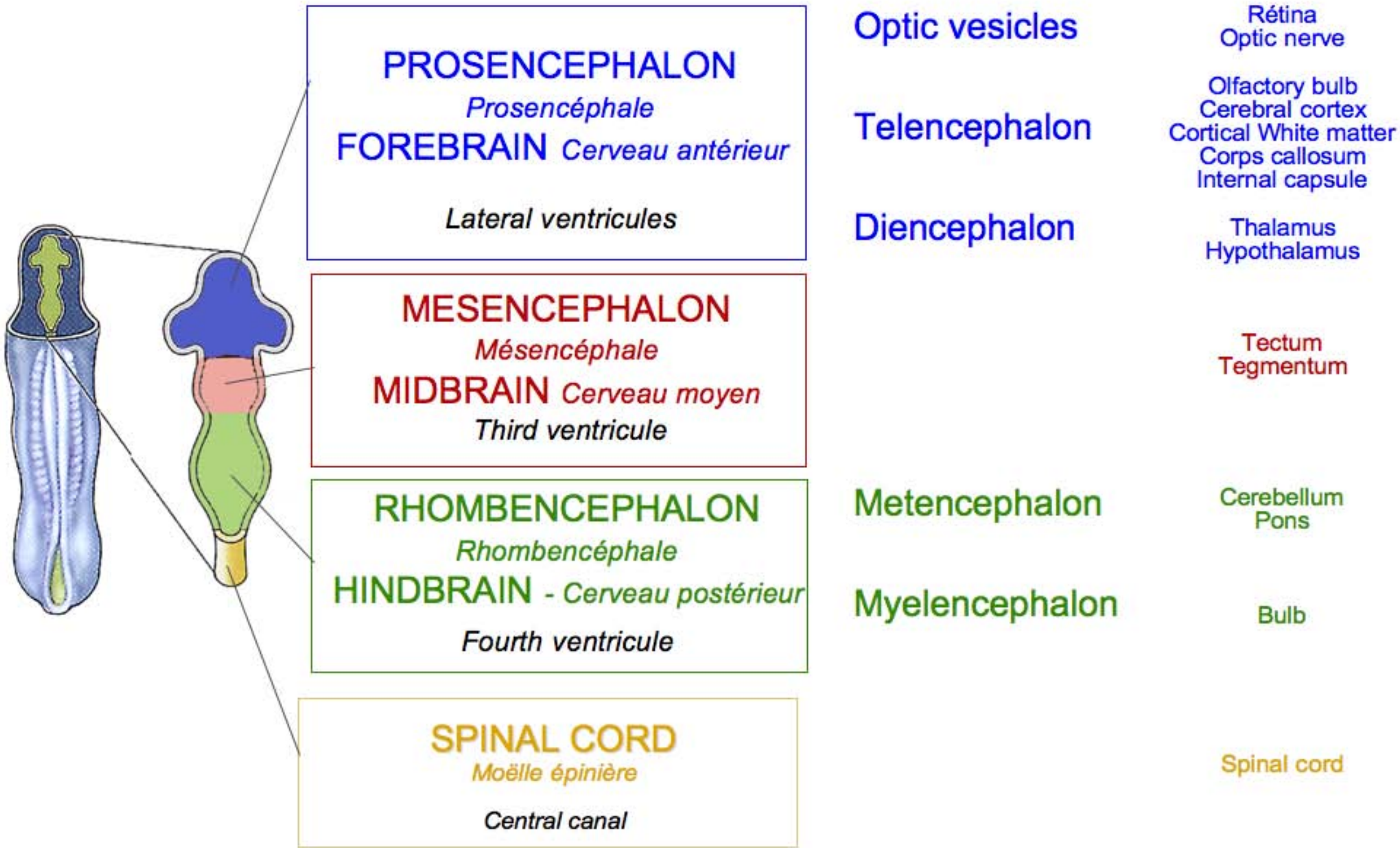
The sandwich model of Gary Banker

Acquisition of neuronal polarity

Synaptogenesis

Neurulation



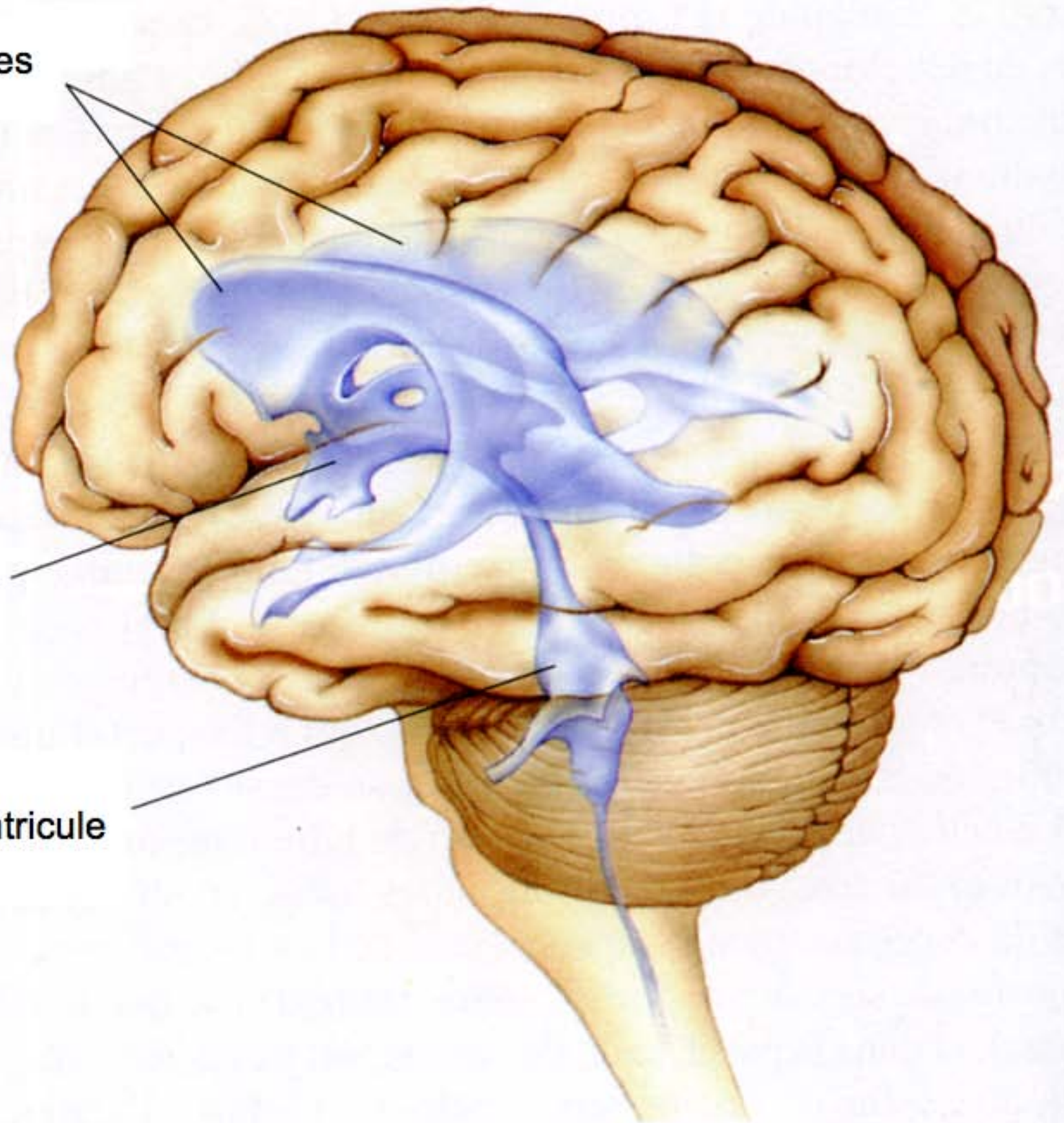


The rostral part of the neural tube differentiates to form the three primitive vesicles at the origin of the brain.

Lateral ventricles

3rd ventricle

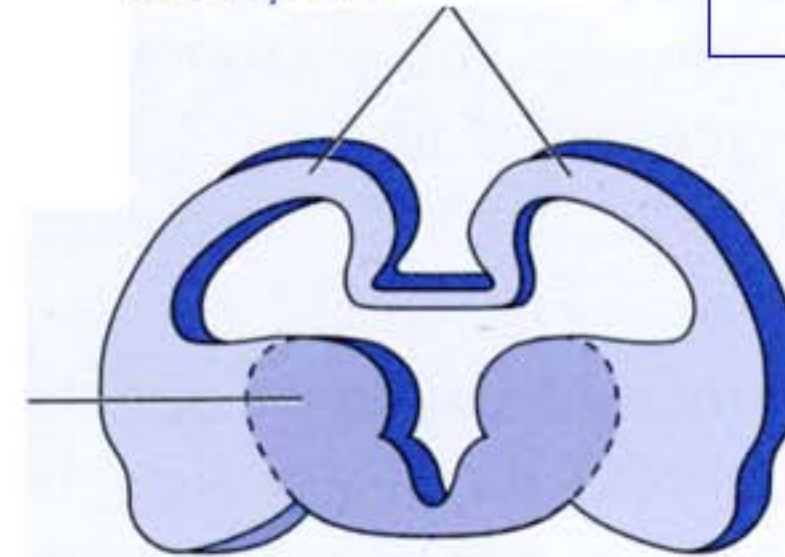
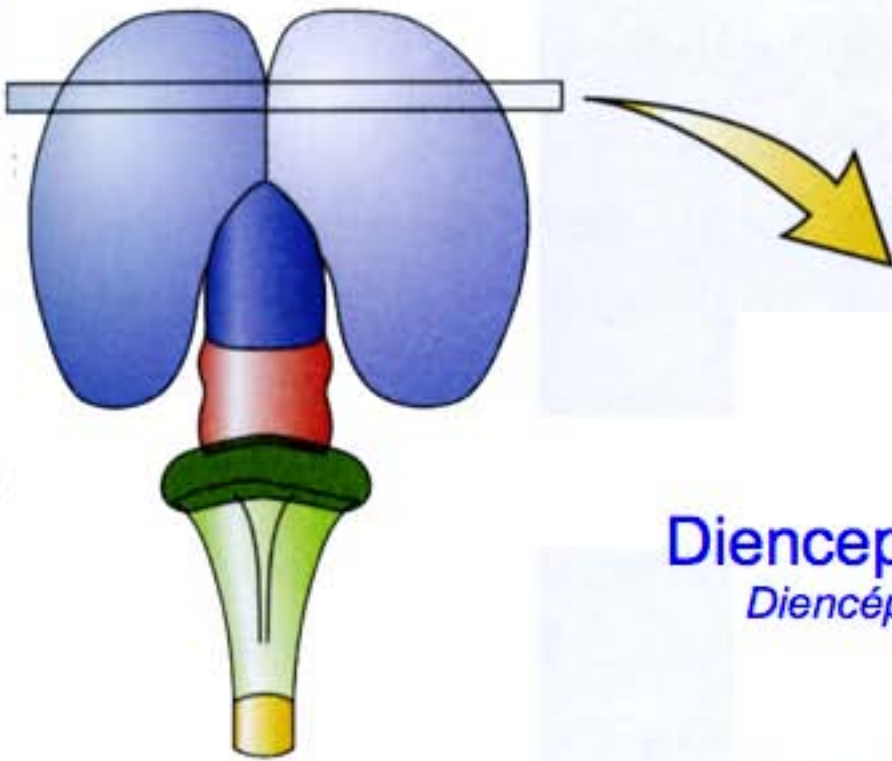
4th ventricle



PROSENCEPHALON
FOREBRAIN
Prosencéphale

Telencephalon
Télencéphale

Diencephalon
Diencephale



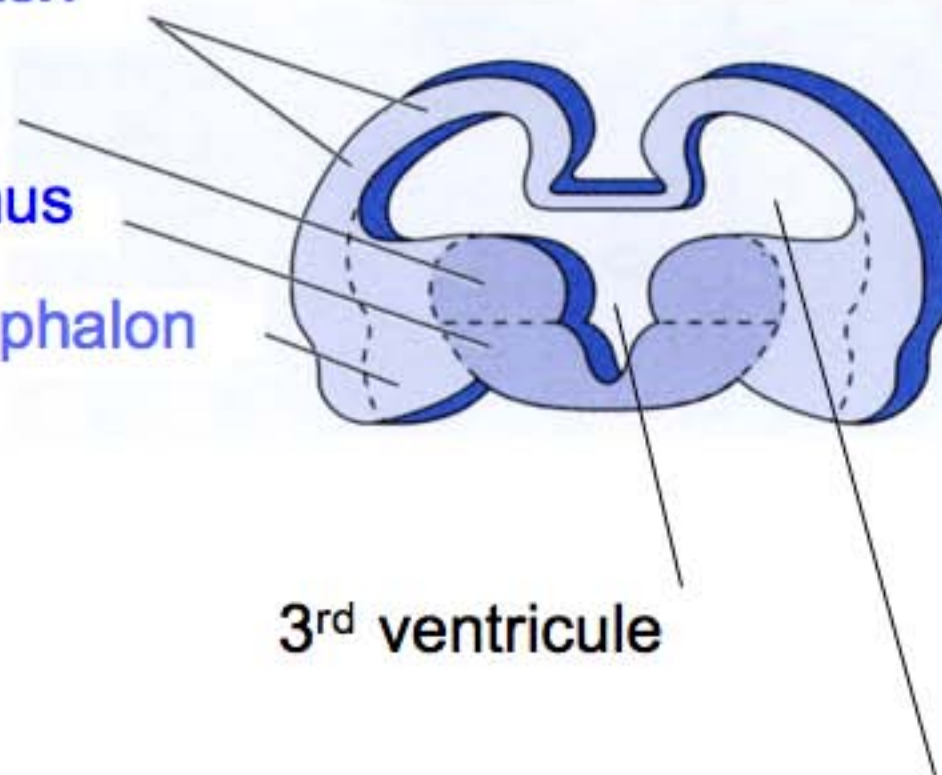
Cerebral cortex

Thalamus
Hypothalamus

Basal telencephalon

3rd ventricle

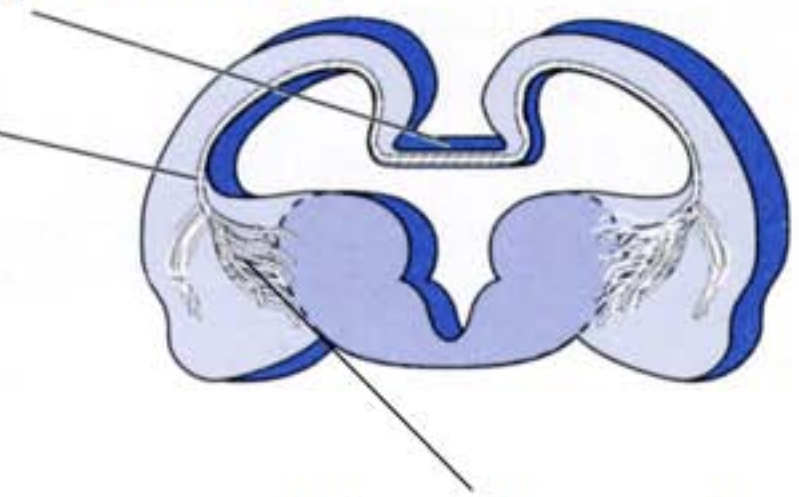
lateral ventricle

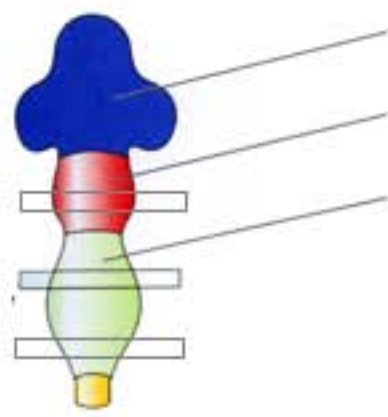


Corpus callosum

White matter

Internal capsule





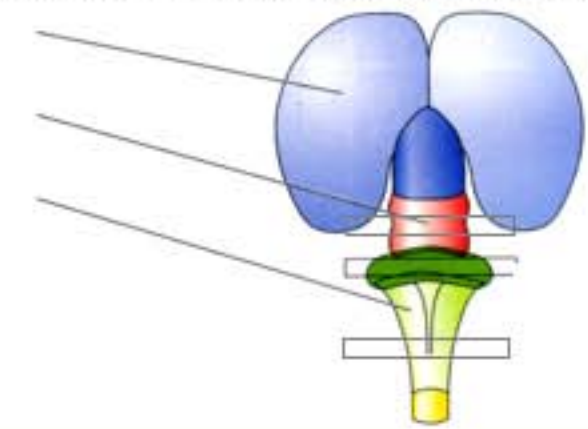
FOREBRAIN - PROSENCEPHALON

MIDBRAIN - MESENCEPHALON

HINDBRAIN - RHOMBENCEPHALON



Differentiation



MESENCEPHALON

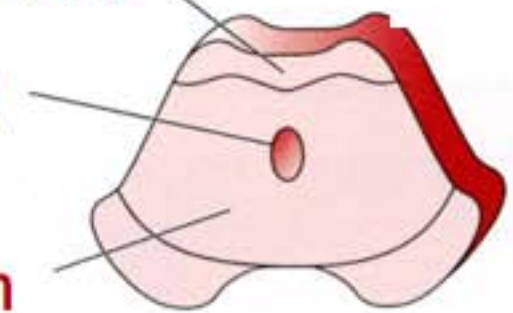
Mésencéphale



Cerebral aqueduct

Tectum

Tegmentum



Rhombencephalic lips



RHOMENCEPHALON

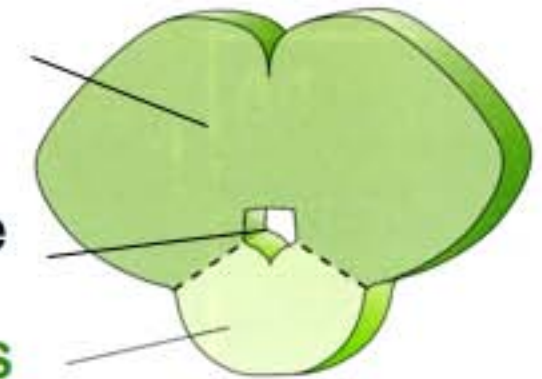
Rhombencéphale



Cerebellum

4th ventricle

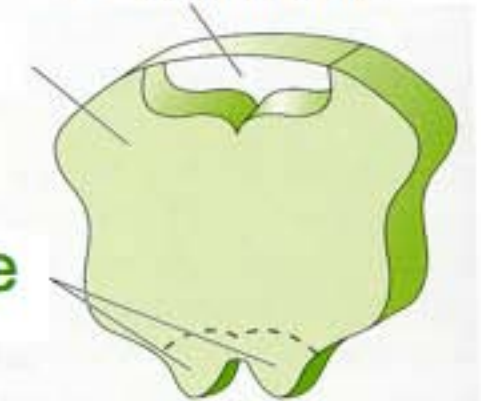
Pons



4th ventricle

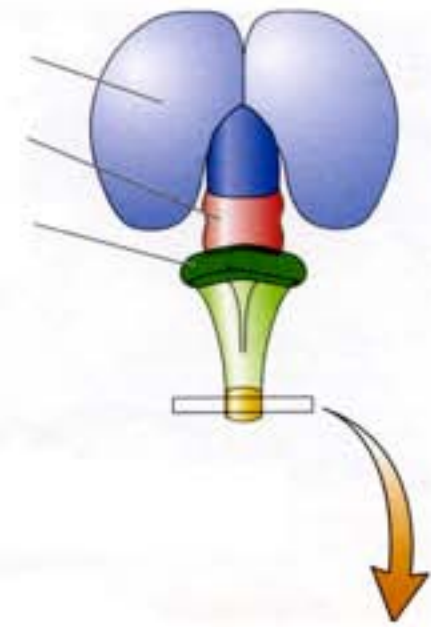
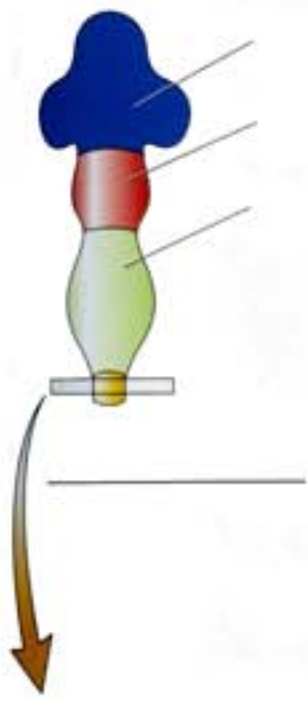
Bulb

Bulb Pyramide



FOREBRAIN - PROSENCEPHALON
MIDBRAIN - MESENCEPHALON
HINDBRAIN - RHOMBENCEPHALON

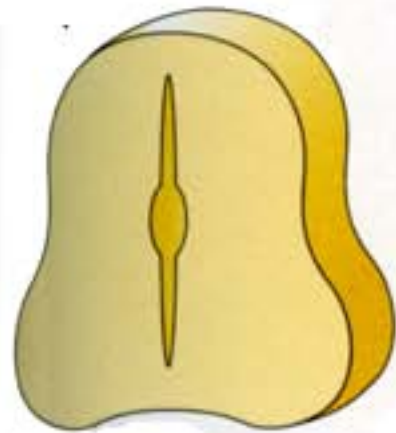
Differentiation



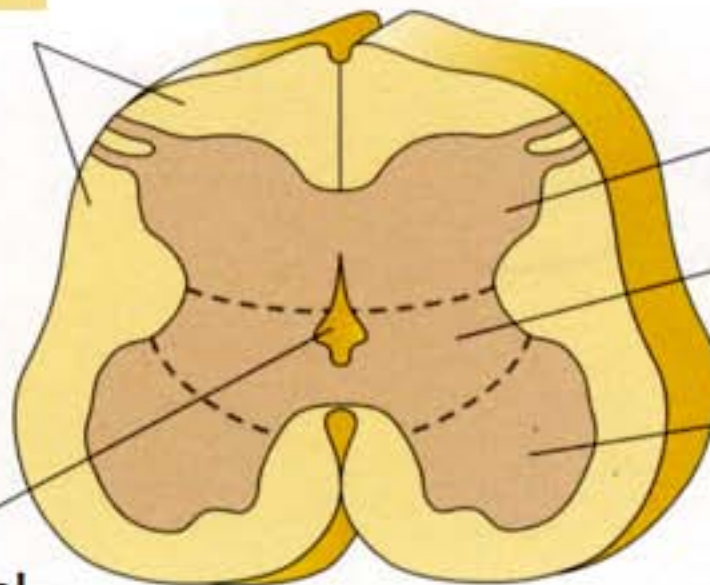
SPINAL CORD

Moëlle épinière

White matter



Spinal canal

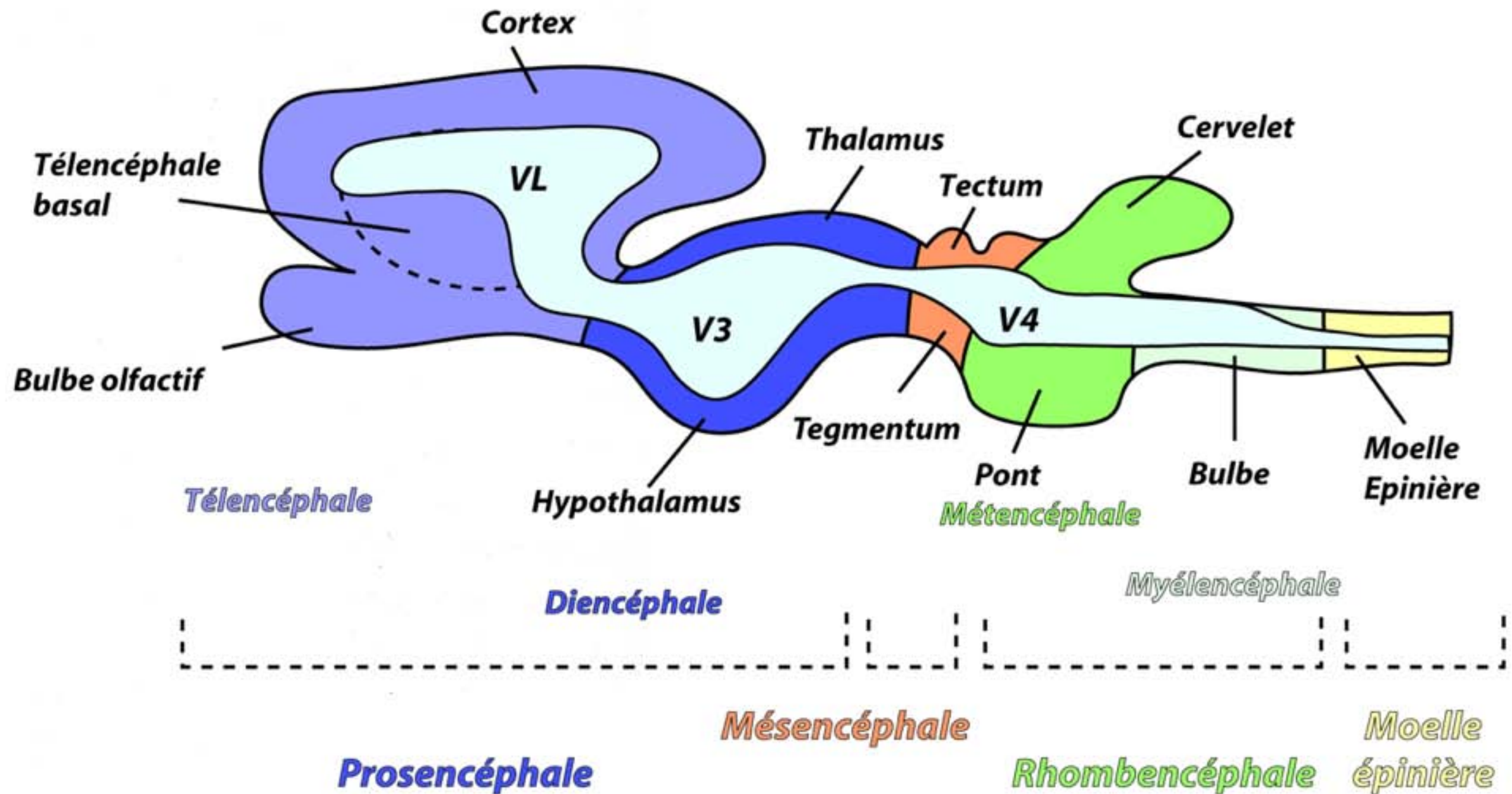


Dorsal horn

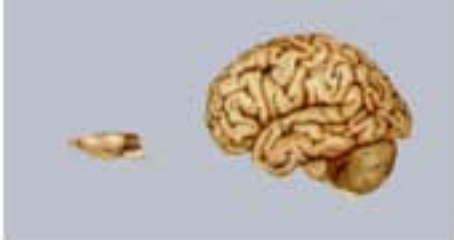
Intermediate zone

Ventral horn

Gray matter

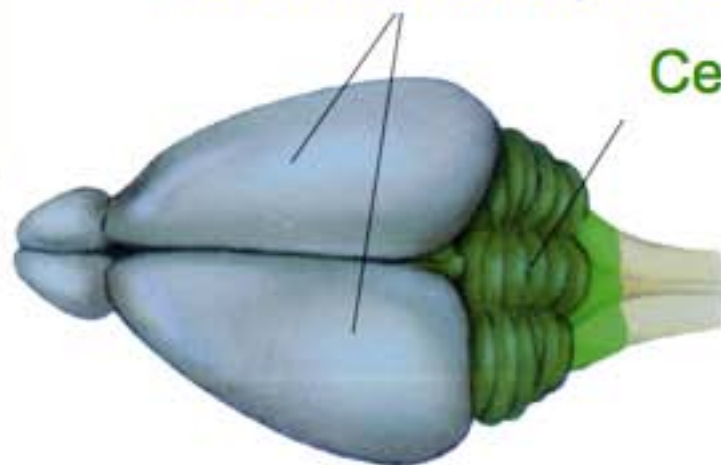


Organisation générale du cerveau des mammifères

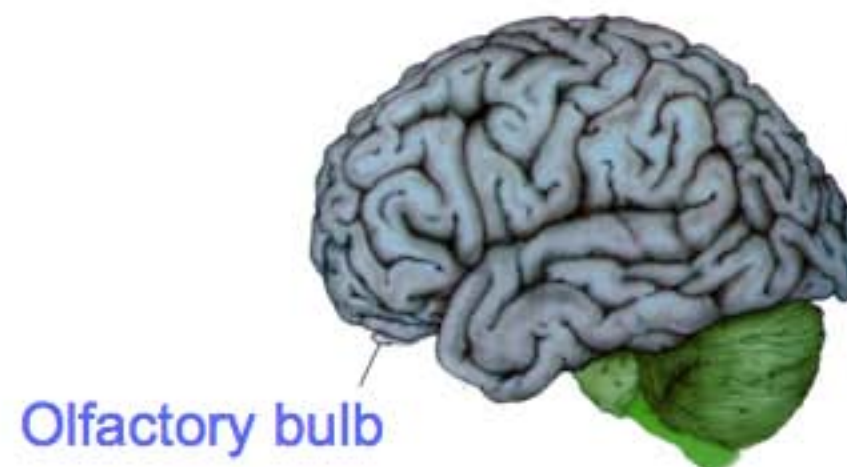
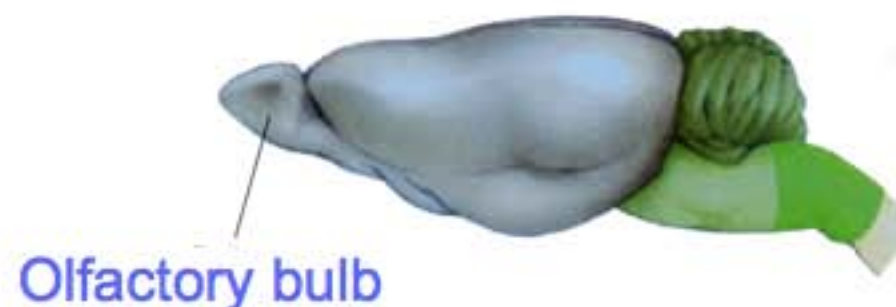
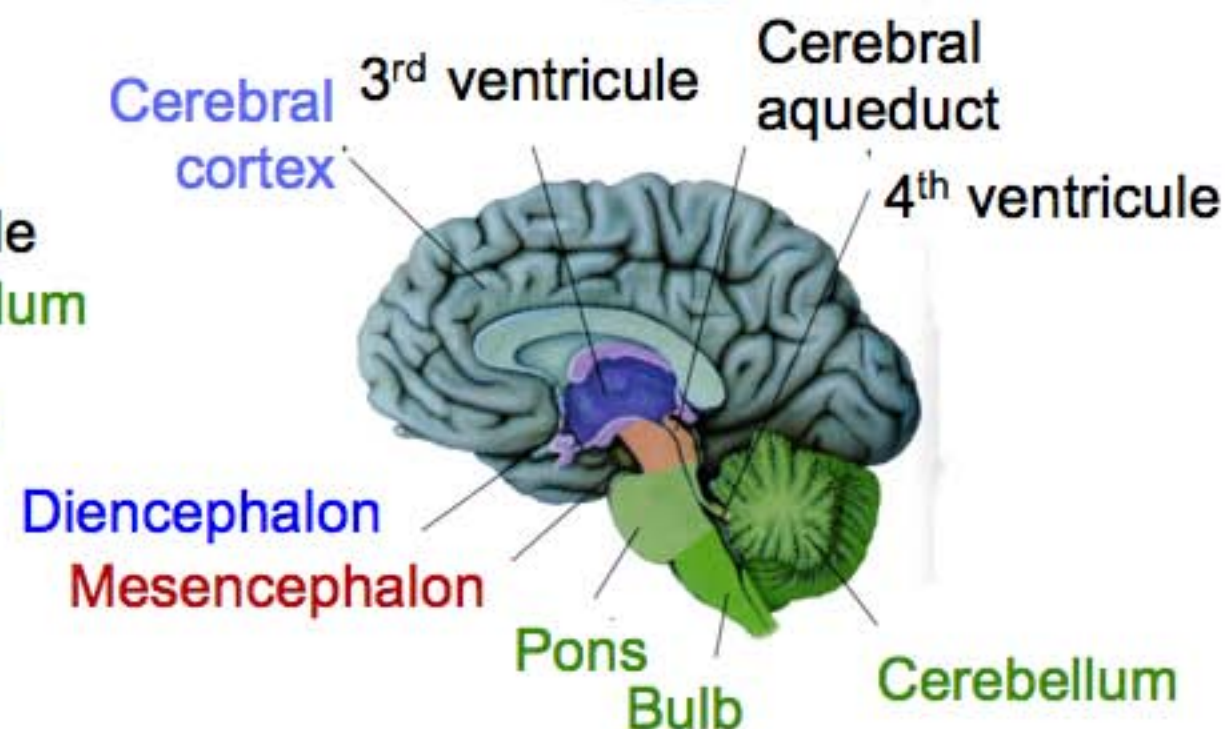
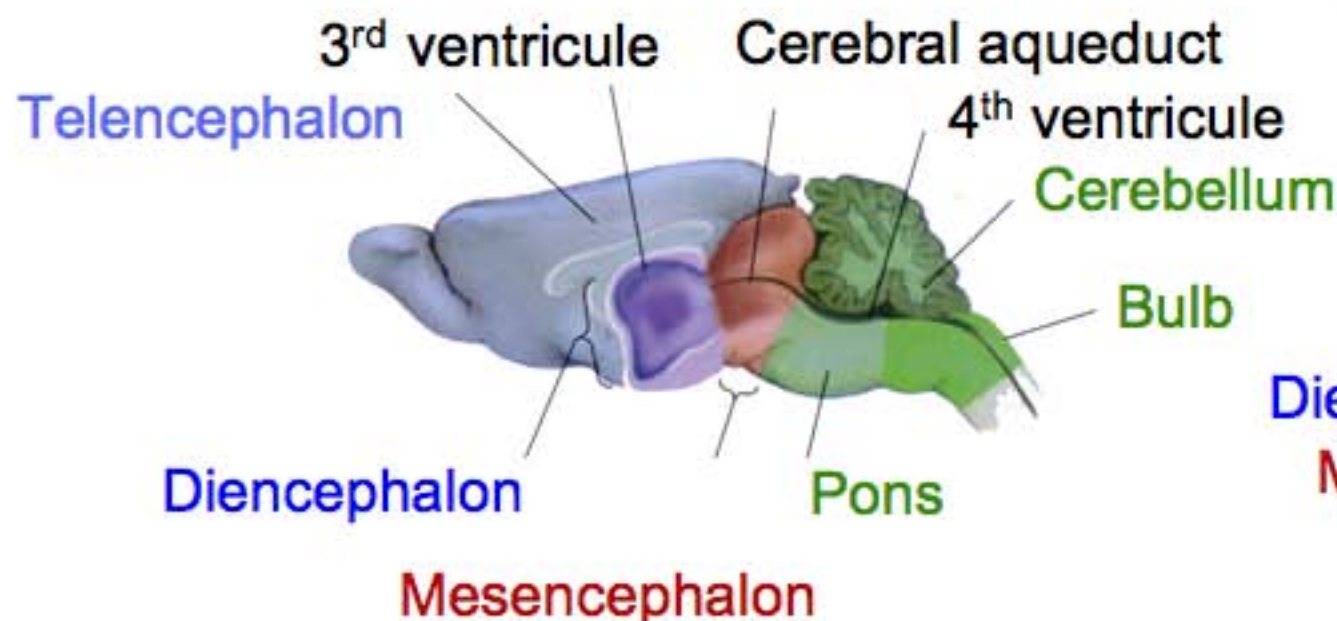


Cerebral hemisphere

Cerebellum



Cerebral hemisphere



PROSENCEPHALON

Prosencéphale

MESENCEPHALON

Mésencéphale

RHOMENCEPHALON

Rhombencéphale

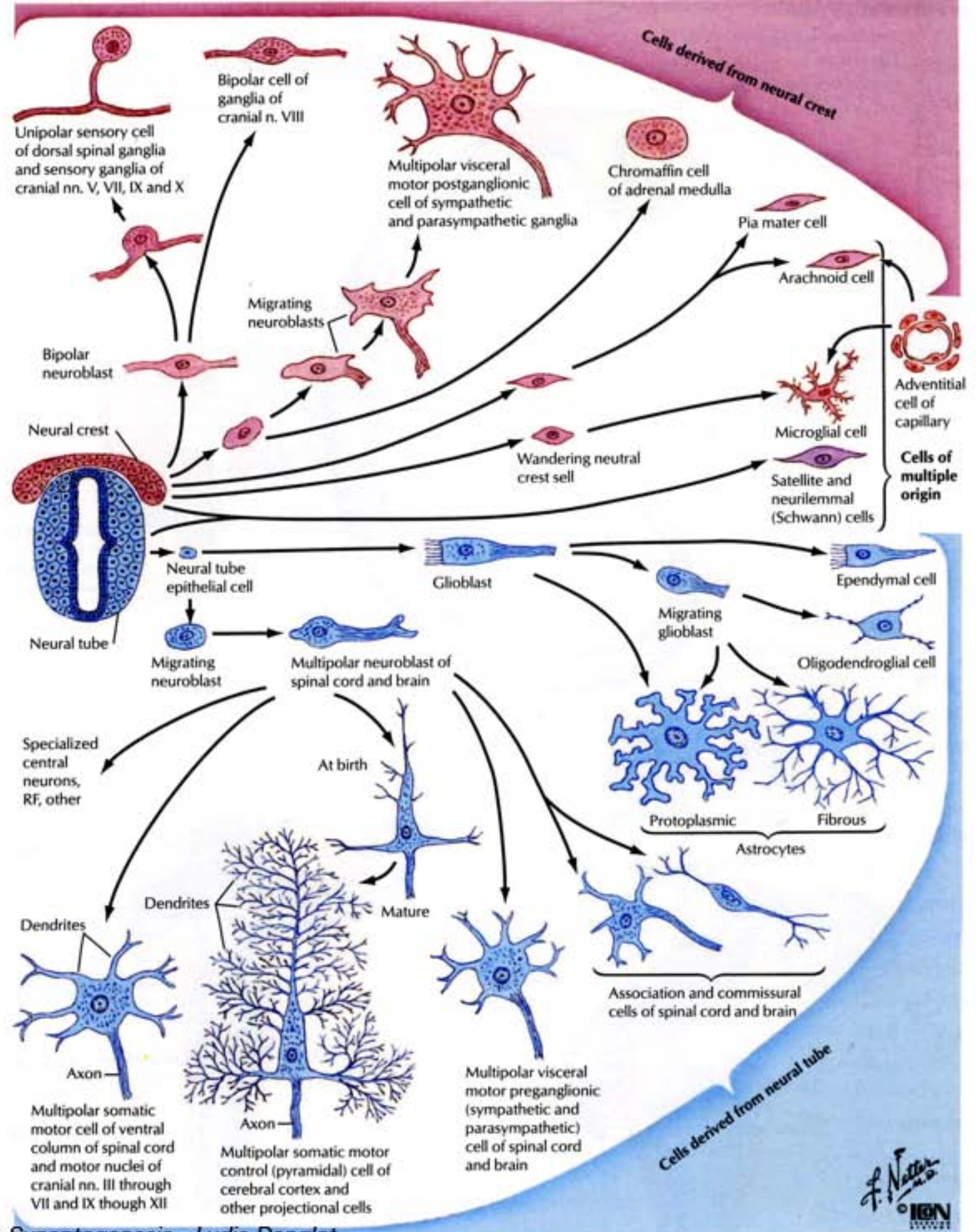
Derived cells from neural tube and neural crest

Neural crest:

- Ganglionic cells (spinal & ANS)
- Chromaffin cells
- Glial cells:
 - Schwann cells
 - Microglia

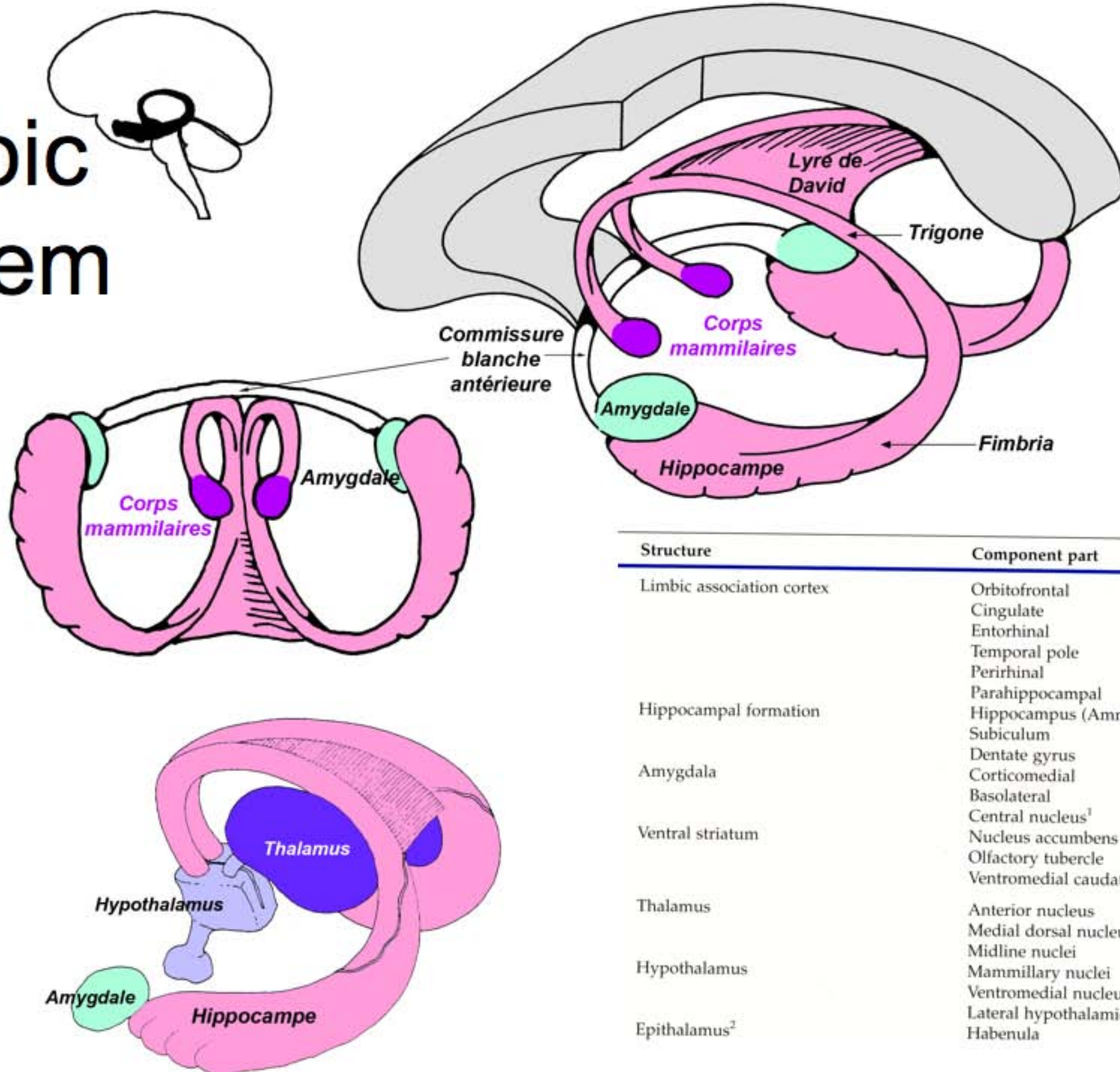
Neural tube:

- Neurons (brain & spinal cord)
- Ependymal cells
- Glial cells:
 - Oligodendrocytes
 - astrocytes



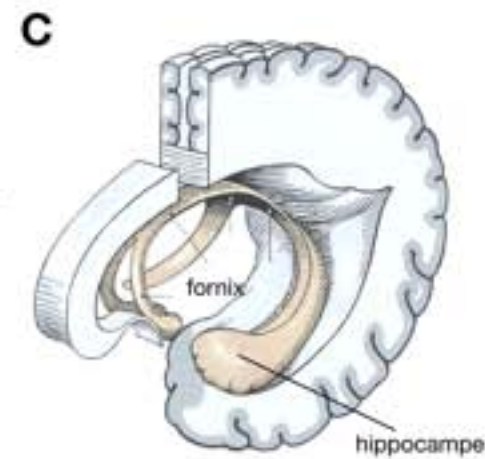
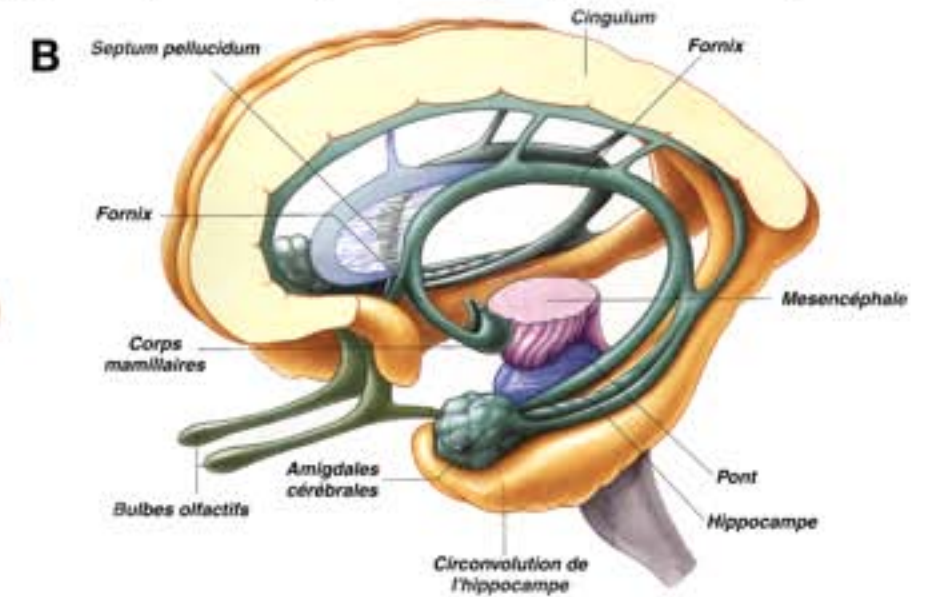
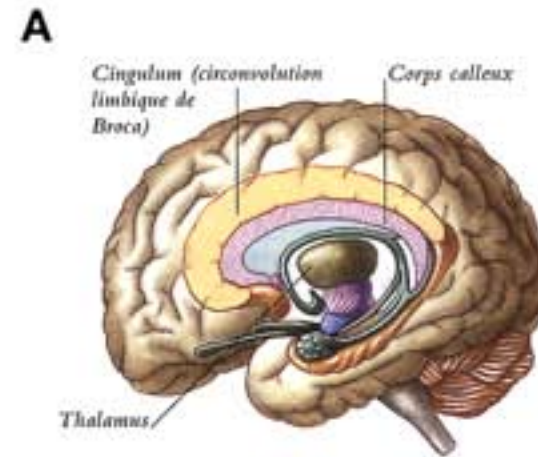
Hippocampus and limbic system

Limbic system

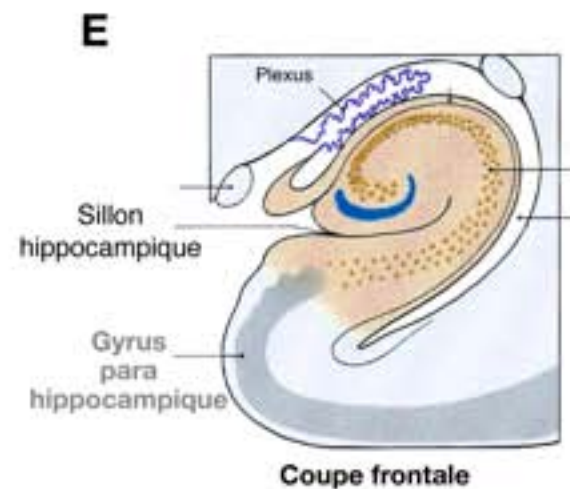
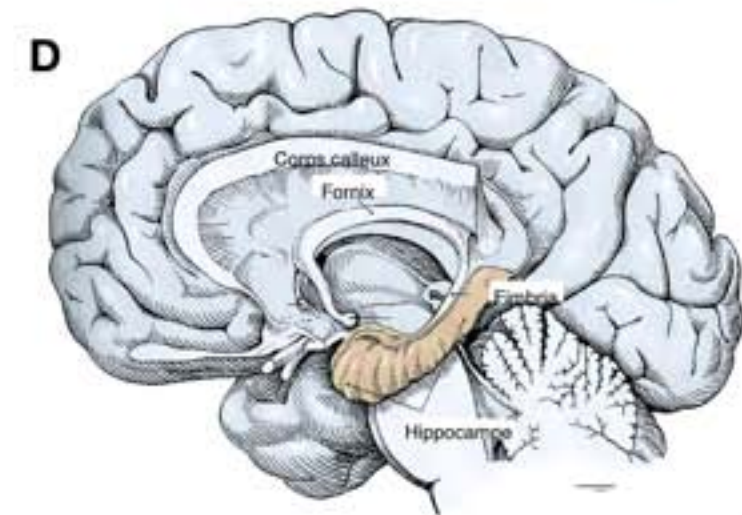


Structure	Component part
Limbic association cortex	Orbitofrontal Cingulate Entorhinal Temporal pole Perirhinal Parahippocampal
Hippocampal formation	Hippocampus (Ammon's horn) Subiculum Dentate gyrus
Amygdala	Corticomедial Basolateral Central nucleus ¹
Ventral striatum	Nucleus accumbens Olfactory tubercle Ventromedial caudate and putamen
Thalamus	Anterior nucleus Medial dorsal nucleus Midline nuclei
Hypothalamus	Mammillary nuclei Ventromedial nucleus Lateral hypothalamic area
Epithalamus ²	Habenula

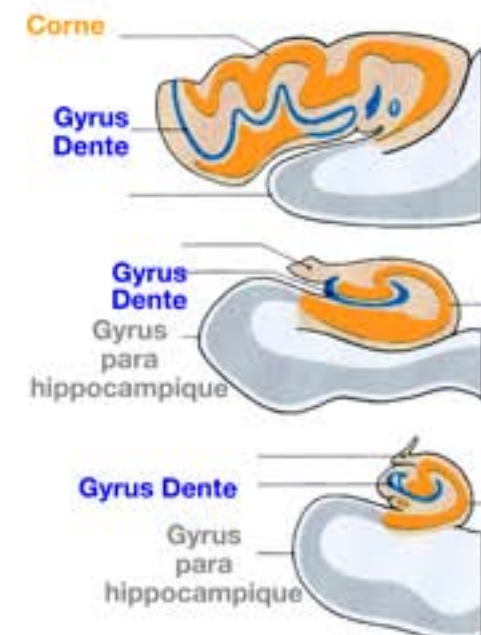
Hippocampus



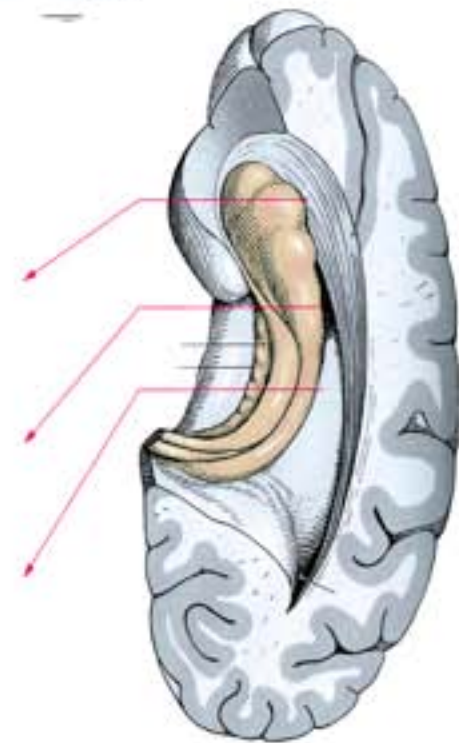
Hippocampe et fornix
(d'après Feneis)



Coupe frontale



Coupes frontales à différents niveaux



Vue supérieure
(d'après Sobotta)

Hippocampus: A cortical structure in the medial portion of the temporal lobe; in humans, concerned with short-term declarative memory, among many other functions.

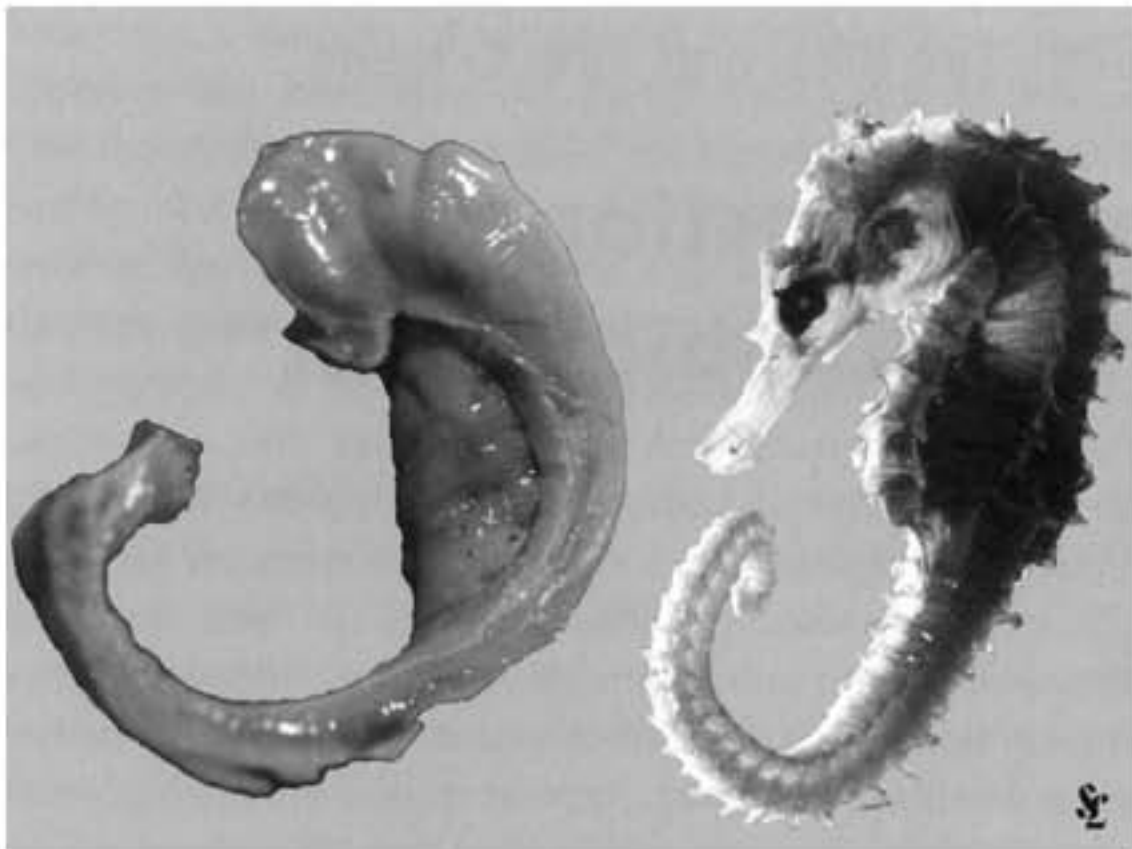
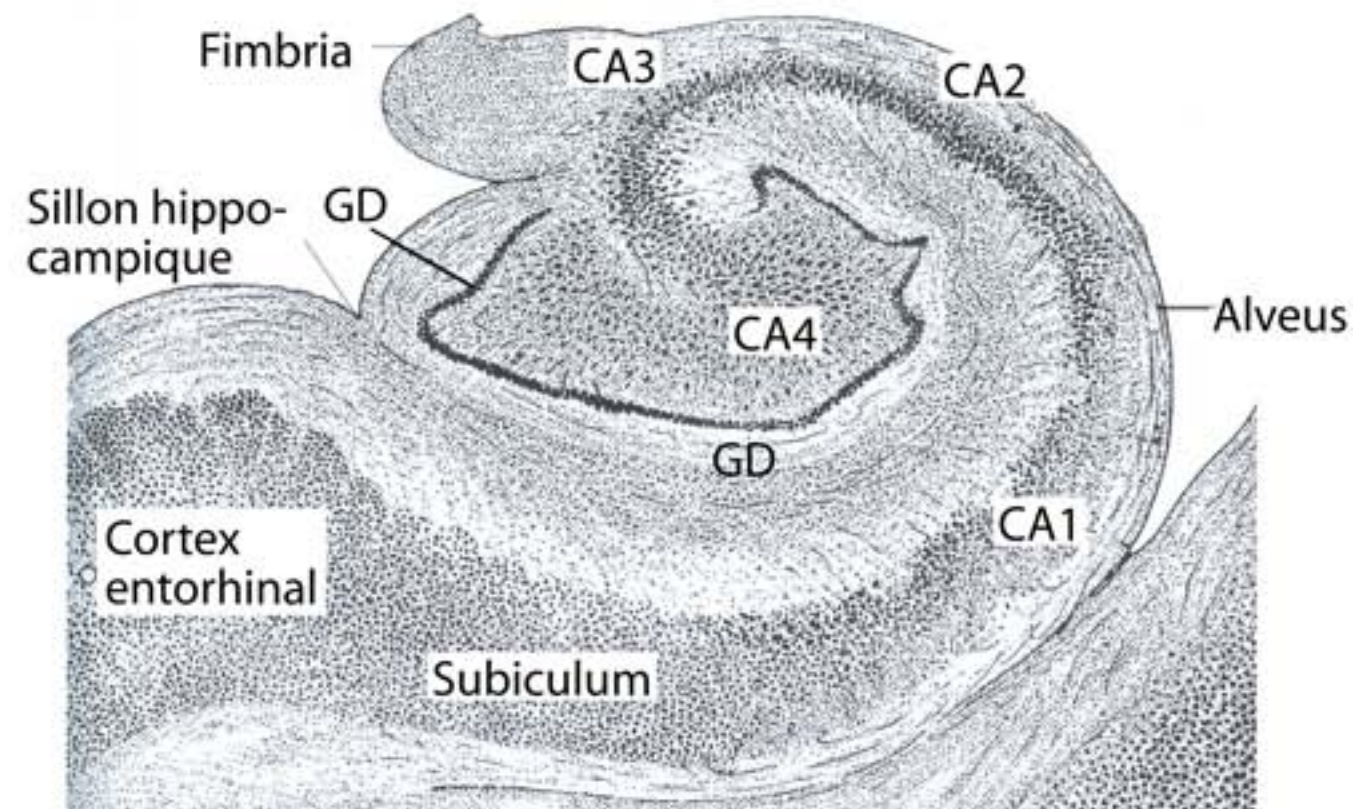
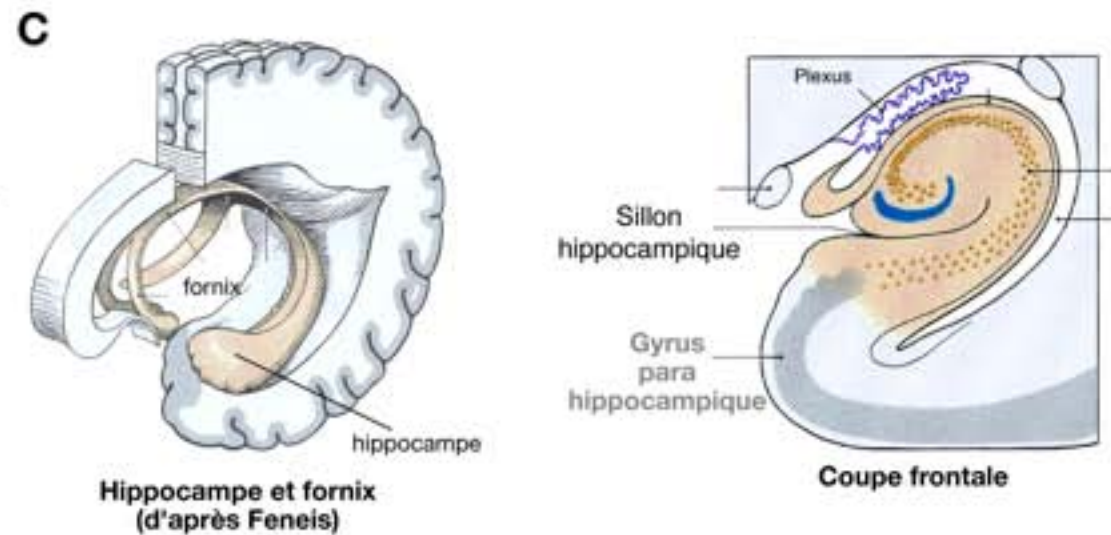
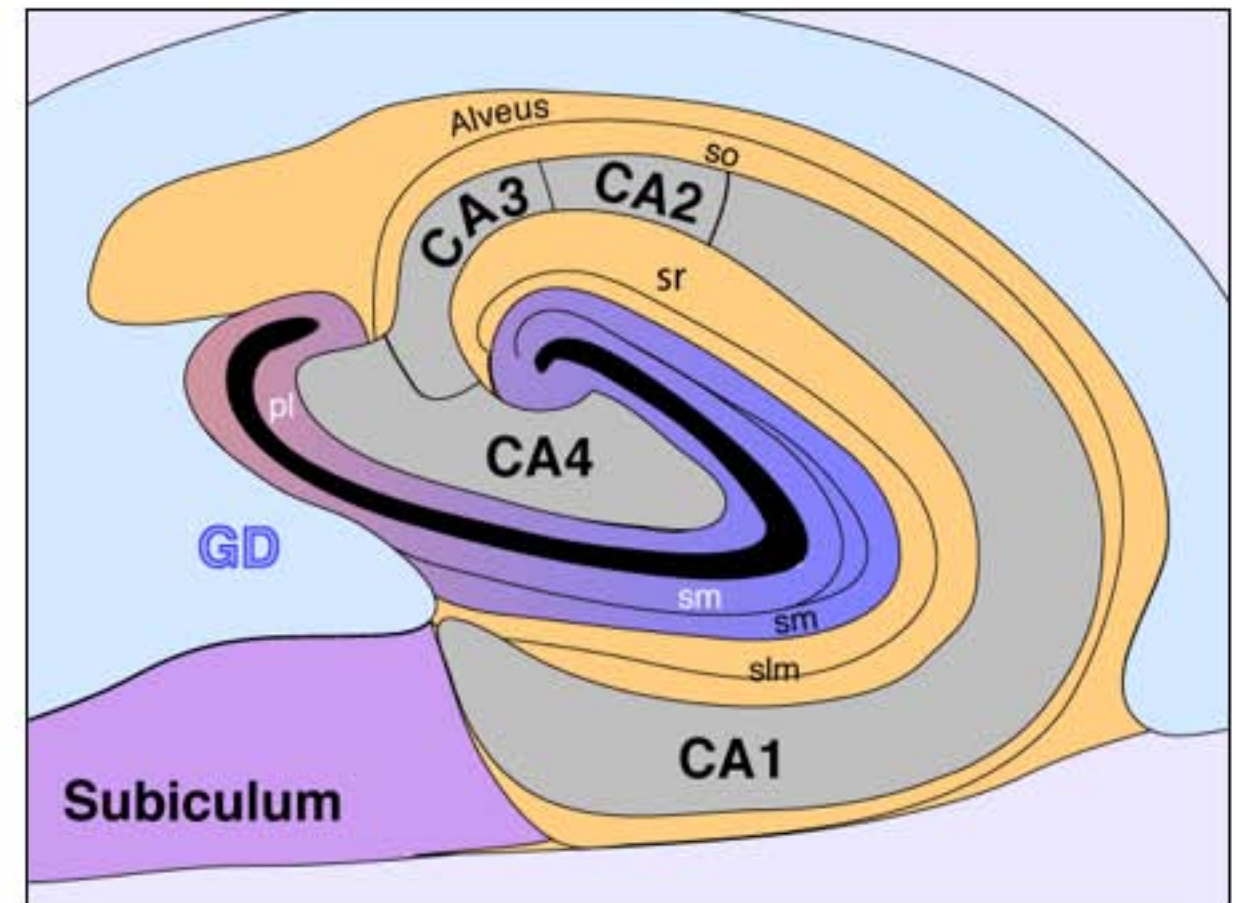
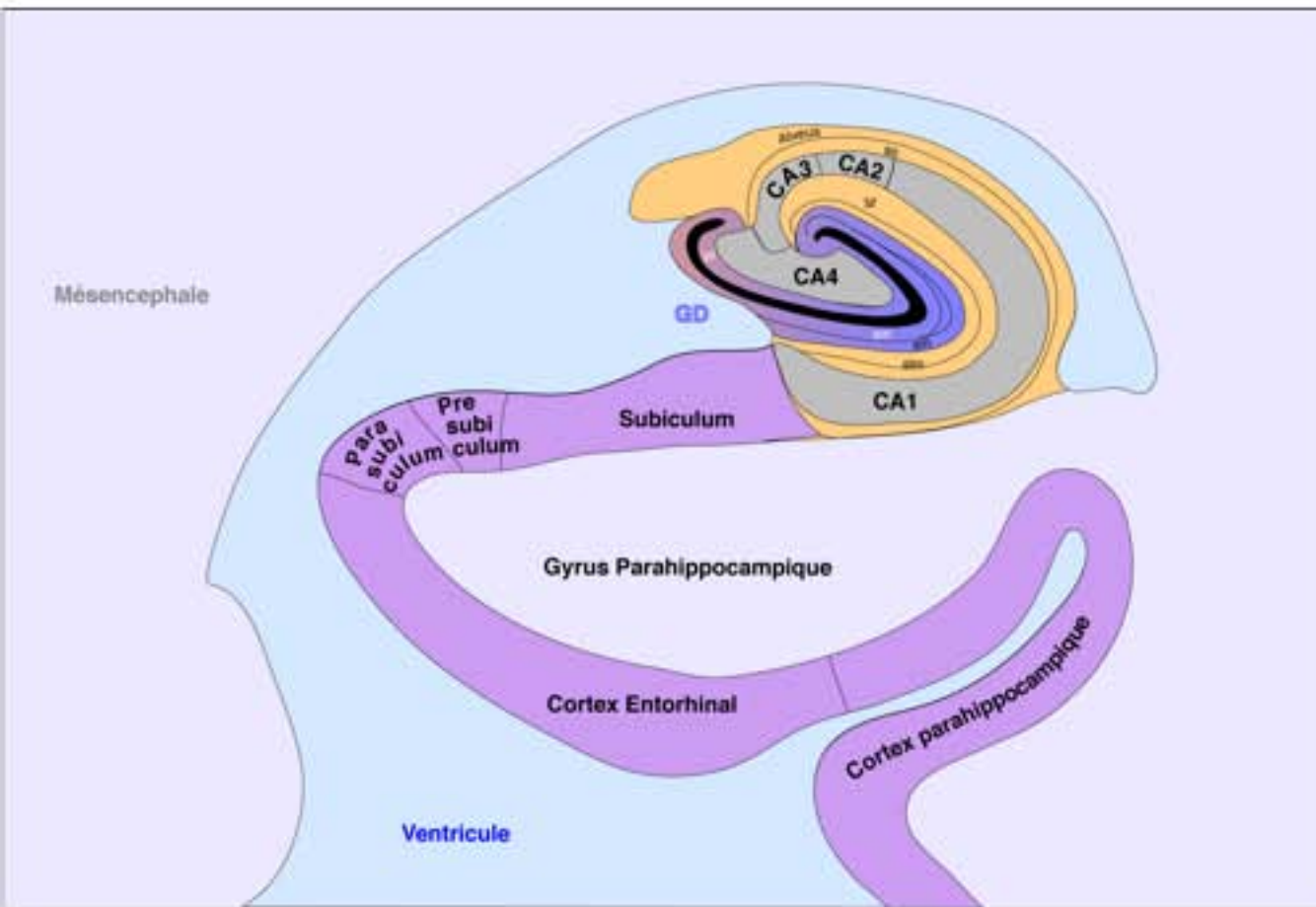


Figure 2-1. Human hippocampus dissected free (left) and compared to a specimen of *Hippocampus leiria* (right). (Source: Courtesy of Professor Laszlo Seress, University of Pecs.)



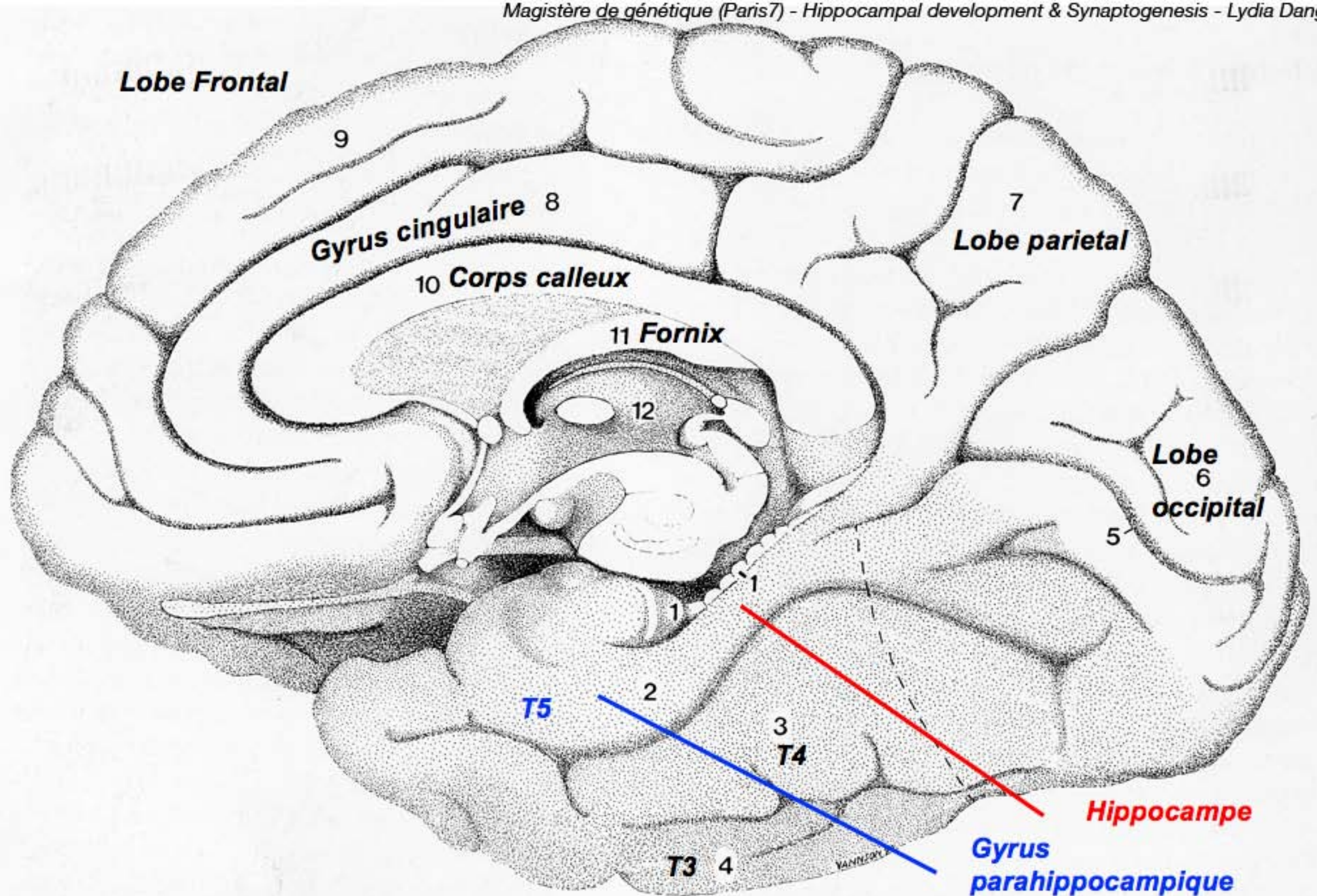
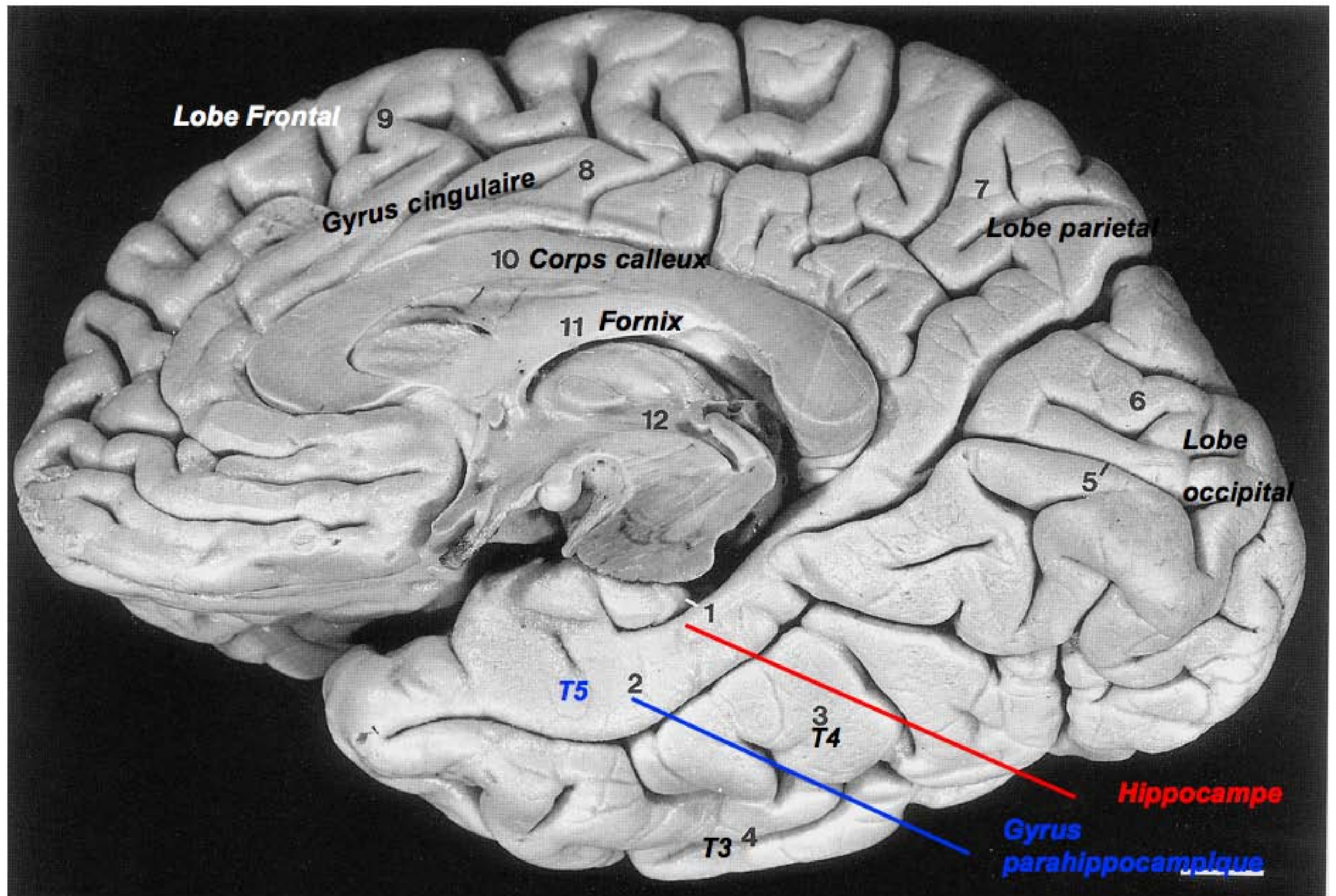


Fig. 1. A Drawing and **B** dissection showing the inferomedial aspect of the right hemisphere. Bar, 10 mm

1, hippocampus, only partly visible on the inferomedial surface of the temporal lobe; 2, parahippocampal gyrus (T5); 3, fusiform gyrus (T4); 4, inferior temporal gyrus (T3);

5, calcarine sulcus; 6, occipital lobe (cuneus); 7, parietal lobe, medial aspect (precuneus); 8, cingulate gyrus; 9, frontal lobe, medial aspect (superior frontal gyrus); 10, corpus callosum; 11, fornix; 12, third ventricle



Putamen

Hippocampe

**Gyrus
parahippocampique**

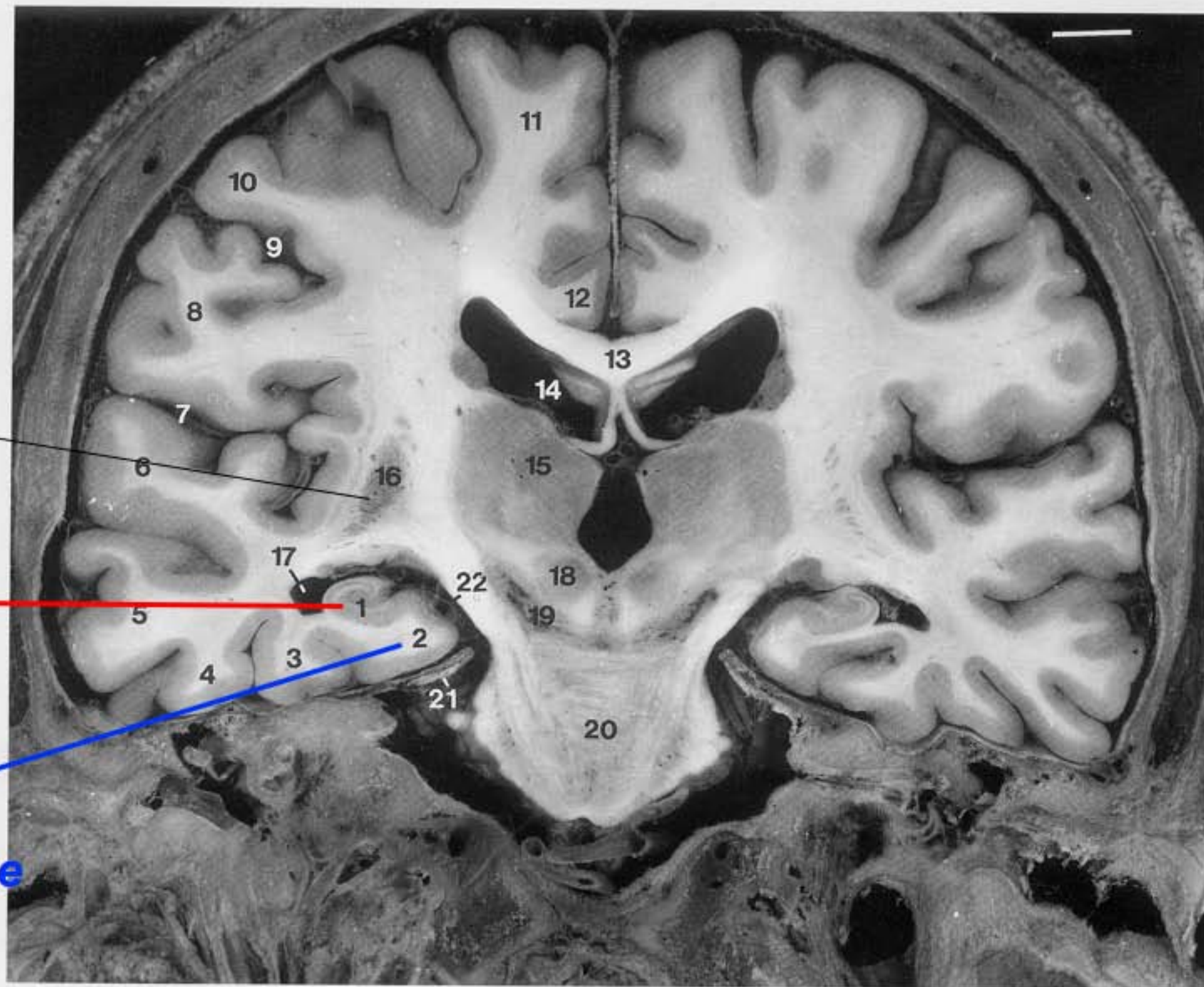


Fig. 2. A, B Coronal section of the brain. **A** Head section. Bar, 10 mm. **B** MRI view, T¹-weighted image

1, hippocampus; 2, parahippocampal gyrus; 3, fusiform gyrus; 4, inferior temporal gyrus; 5, middle temporal gyrus; 6, superior temporal gyrus; 7, lateral fissure; 8, postcentral gyrus; 9, central sulcus; 10, precentral gyrus; 11, superior

frontal gyrus; 12, cingulate gyrus; 13, corpus callosum; 14, lateral ventricle; 15, thalamus; 16, putamen; 17, temporal (inferior) horn of the lateral ventricle; 18, red nucleus; 19, substantia nigra; 20, pons; 21, tentorium cerebelli; 22, ambient cistern

The human hippocampus, Henri M. Duvernoy.

Noyau Caude

Putamen

Pallidum

Amygdale

Hippocampe

**Gyrus
parahippocampique**

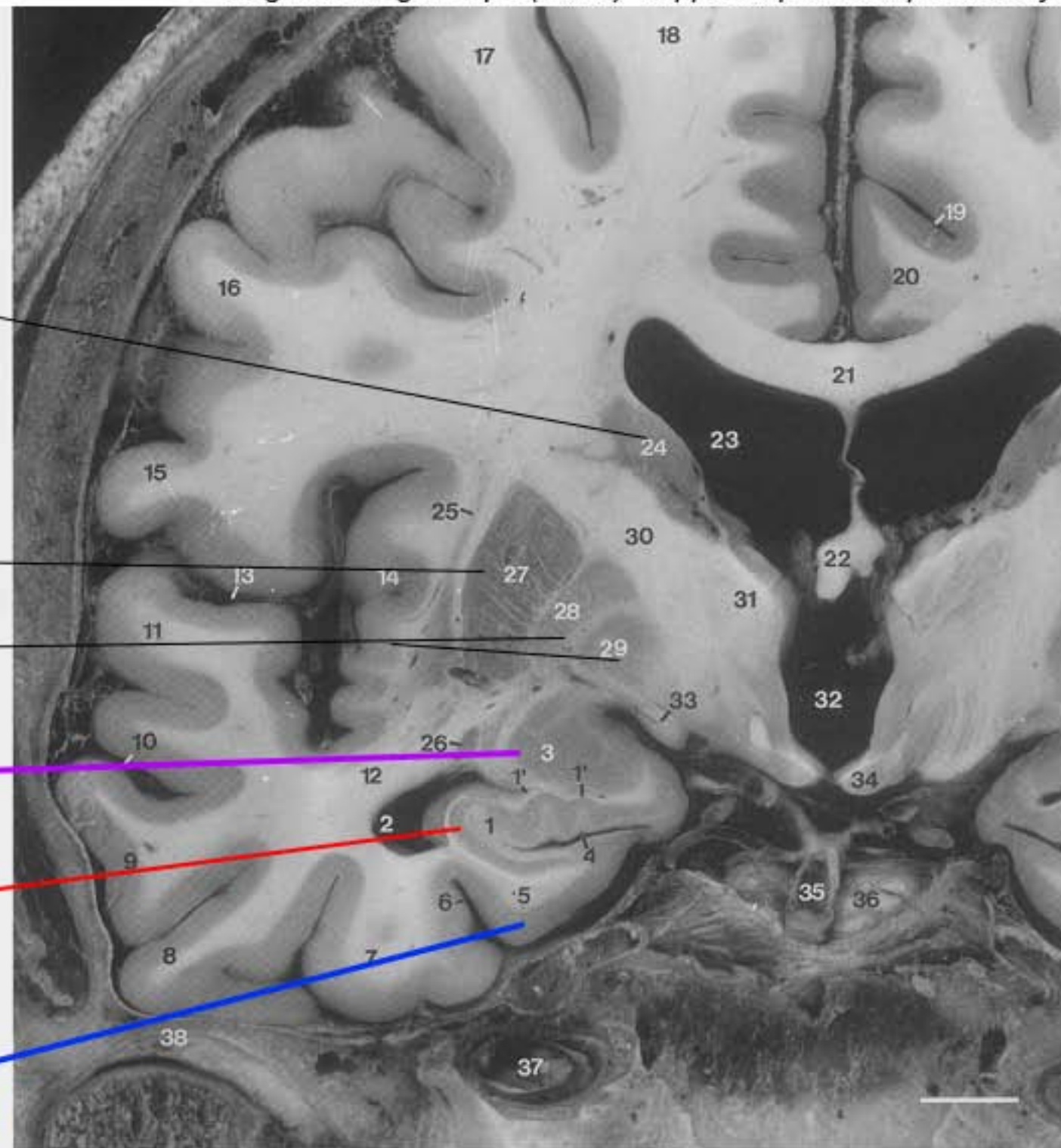
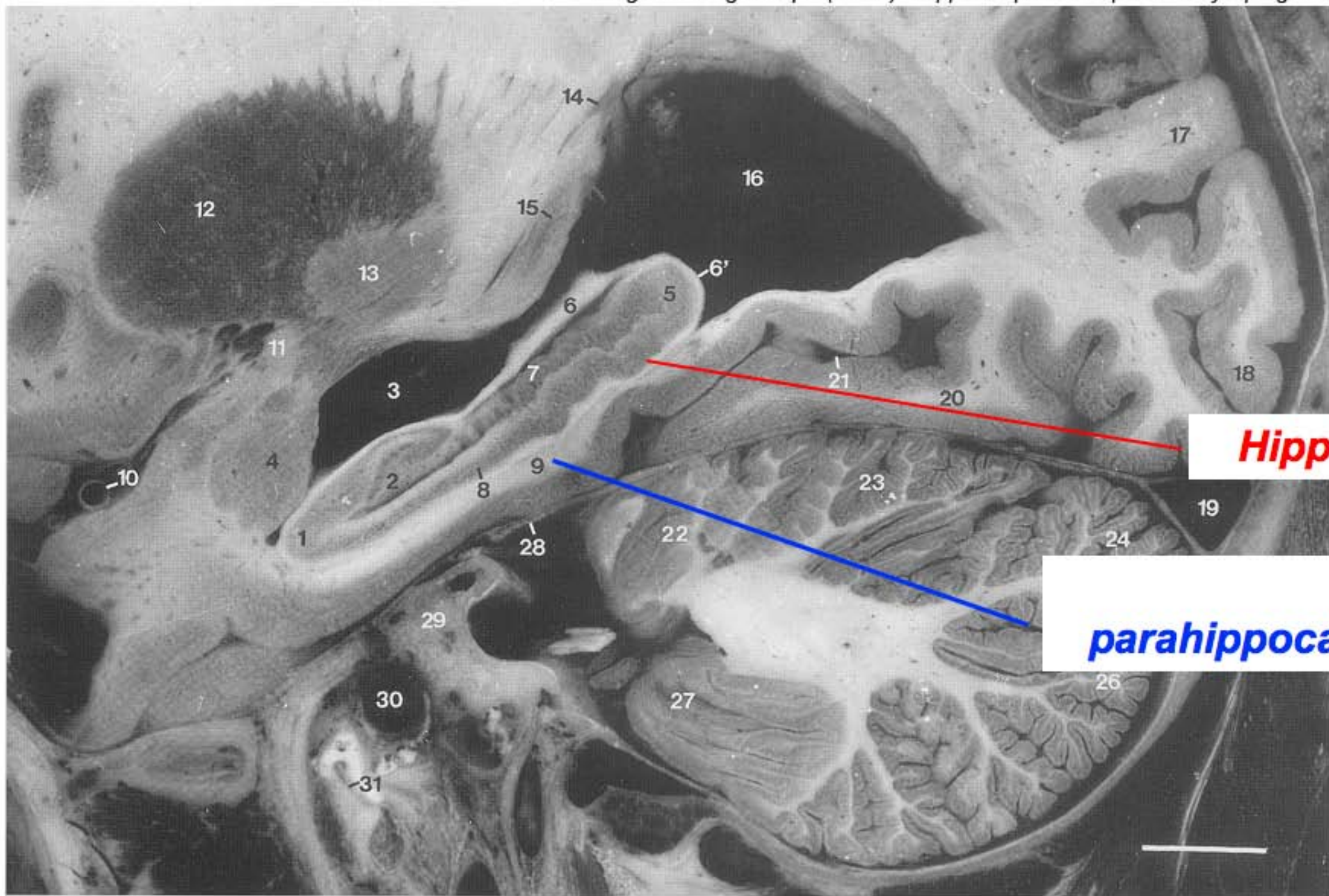


Fig. 84. E Coronal head section. Anterior view of the section.
Bar, 10 mm

1, hippocampal head; 1', internal digitations (digitations hippocampi); 2, temporal (inferior) horn of the lateral ventricle; 3, amygdala; 4, uncus sulcus; 5, parahippocampal gyrus; 6, collateral sulcus; 7, fusiform gyrus; 8, inferior temporal gyrus; 9, middle temporal gyrus; 10, superior temporal sulcus; 11, superior temporal gyrus; 12, temporal stem; 13, lateral fissure; 14, insula; 15, postcentral gyrus; 16, precentral gyrus; 17, middle frontal gyrus; 18, superior frontal gyrus; 19, cin-

gulate sulcus; 20, cingulate gyrus; 21, corpus callosum; 22, fornix; 23, lateral ventricle; 24, caudate nucleus; 25, claustrum; 26, tail of caudate nucleus; 27, putamen; 28, globus pallidus, lateral part; 29, globus pallidus, medial part; 30, internal capsule, posterior limb; 31, ventral anterior thalamic nucleus; 32, third ventricle; 33, optic tract; 34, mamillary body; 35, basilar artery; 36, pons; 37, internal carotid artery; 38, temporomandibular joint



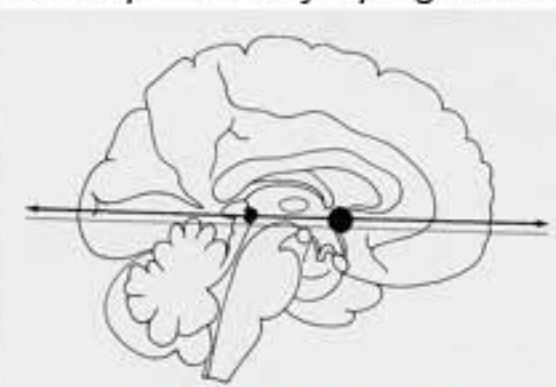
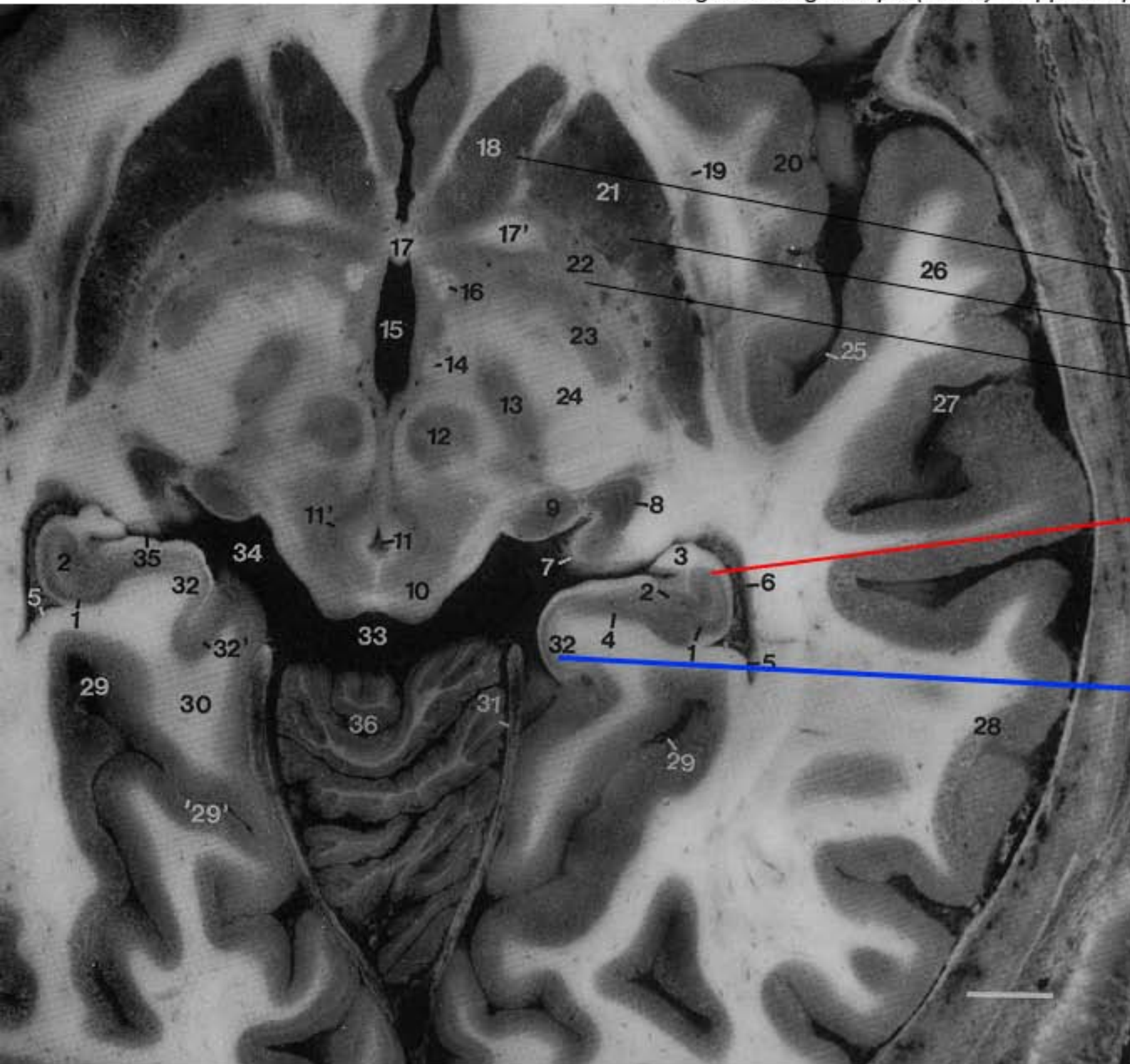
Hippocampe

**Gyrus
parahippocampique**

Fig. 97. F Head section. Bar, 10 mm

1, hippocampal head, cornu Ammonis; 2, hippocampal head, gyrus dentatus; 3, temporal (inferior) horn of the lateral ventricle; 4, amygdala; 5, hippocampal body, cornu Ammonis; 6, fimbria; 6', alveus; 7, margo denticulatus (gyrus dentatus); 8, subiculum; 9, parahippocampal gyrus; 10, middle cerebral artery; 11, anterior commissure, lateral part; 12, putamen; 13, globus pallidus, lateral part; 14, caudate nucleus; 15, pul-

vinar; 16, lateral ventricle; 17, middle occipital gyrus; 18, inferior occipital gyrus; 19, transverse sinus; 20, fusiform gyrus; 21, collateral sulcus; 21', anterior calcarine sulcus; 21'', calcar avis; 22, quadrangular lobule; 23, simple lobule; 24, superior semilunar lobule; 25, horizontal fissure; 26, inferior semilunar lobule; 27, biventer lobule; 28, tentorium cerebelli; 29, temporal, petrous part; 30, internal carotid artery; 31, auditory tube



Noyau Caude

Putamen

Pallidum

Hippocampe

**Gyrus
parahippocampique**

1, hippocampal body, cornu Ammonis; 2, hippocampal body, gyrus dentatus; 3, fimbria; 4, subiculum; 5, collateral eminence; 6, temporal (inferior) horn of the lateral ventricle; 7, pulvinar; 8, lateral geniculate body; 9, medial geniculate body; 10, superior colliculus; 11, cerebral aqueduct; 11', periaqueductal grey matter; 12, red nucleus; 13, substantia nigra; 14, mamillothalamic tract; 15, third ventricle; 16, column of fornix; 17, anterior commissure, medial part; 17', anterior commissure, lateral part; 18, caudate nucleus; 19, claustrum; 20, insula; 21, putamen; 22, globus pallidus, lateral part; 23, globus pallidus, medial part; 24, internal capsule, posteri-

or limb; 25, lateral fissure; 26, superior temporal gyrus; 27, superior temporal sulcus; 28 middle temporal gyrus; 29 collateral sulcus; 29', lingual sulcus; 30, lingual gyrus; 31, tentorium cerebelli; 32, parahippocampal gyrus; 32', anterior calcarine sulcus; 33, quadrigeminal cistern; 34, ambient cistern; 35, wing of ambient cistern; 36, culmen

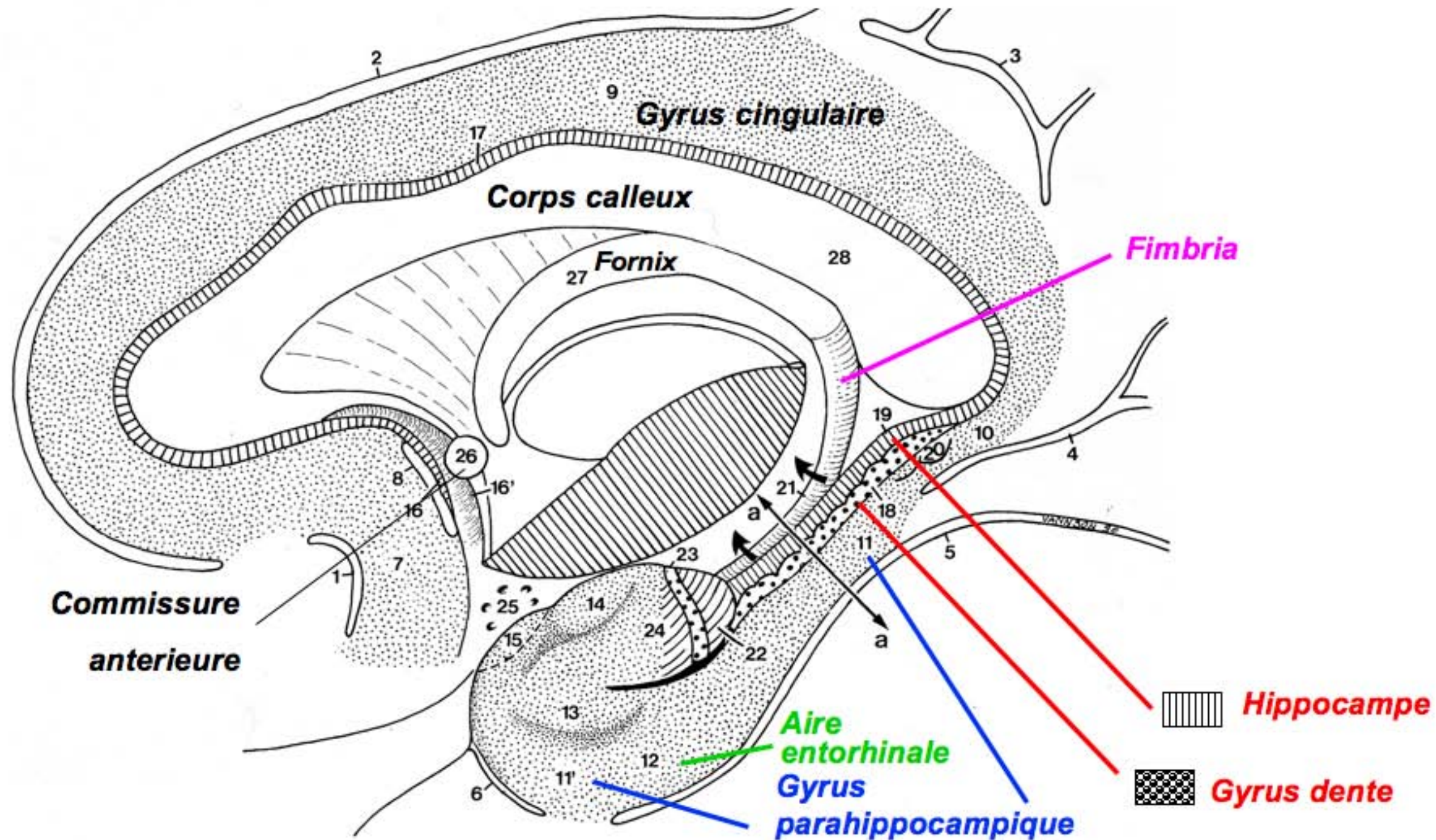


Fig. 4. A Drawing and **B** dissection showing a sagittal section, right hemisphere. The limbic lobe is separated from the isocortex by the limbic fissure and may be divided into two gyri: the limbic and intralimbic gyri. The line a-a indicates the plane of the section on Fig. 5. Bar, 7.7 mm

Limbic fissure: 1, anterior paraolfactory sulcus (subcallosal sulcus); 2, cingulate sulcus; 3, subparietal sulcus; 4, anterior calcarine sulcus; 5, collateral sulcus; 6, rhinal sulcus. Limbic gyrus: 7, subcallosal gyrus; 8, posterior paraolfactory sulcus; 9, cingulate gyrus; 10, isthmus; 11, parahippocampal gyrus,

posterior part; 11', parahippocampal gyrus, anterior part (piriform lobe). Piriform lobe: 12, entorhinal area; 13, ambient gyrus; 14, semilunar gyrus; 15, prepiriform cortex. Intralimbic gyrus: 16, prehippocampal rudiment; 16', paraterminal gyrus; 17, indusium griseum. Hippocampus: 18, gyrus dentatus; 19, cornu Ammonis; 20, gyri of Andreas Retzius; 21, fimbria (displaced upwards, arrows); 22, uncus apex; 23, band of Giacomini; 24, uncinatus gyrus; 25, anterior perforated substance; 26, anterior commissure; 27, fornix; 28, corpus callosum

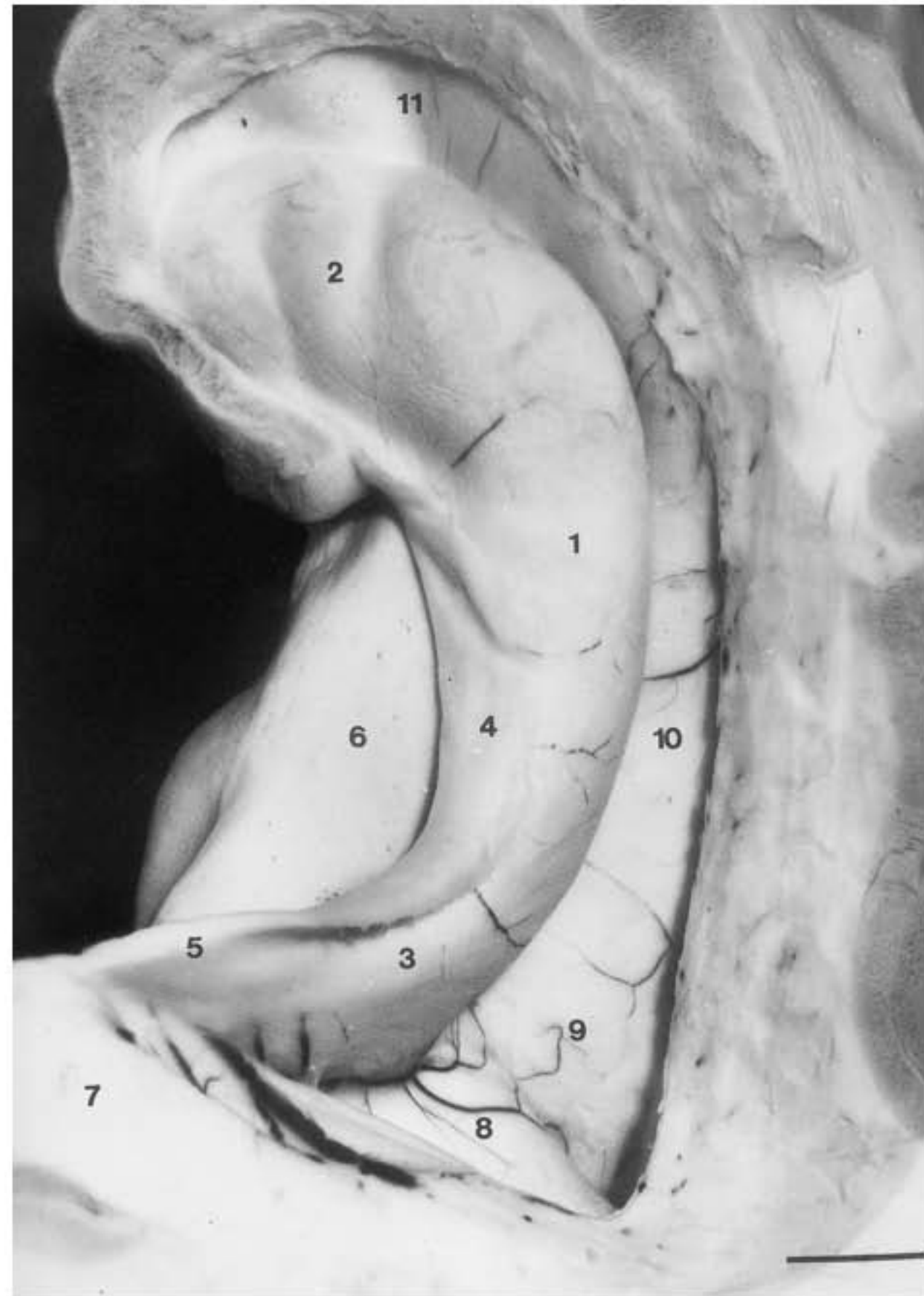


Fig. 3. Intraventricular aspect of the hippocampus. The temporal horn has been opened and the choroid plexuses removed. Bar, 6.5 mm
 1, hippocampal body; 2, head and digitations hippocampi (internal digitations); 3, hippocampal tail; 4, fimbria; 5, crus of fornix; 6, subiculum; 7, splenium of the corpus callosum; 8, calcar avis; 9, collateral trigone; 10, collateral eminence; 11, uncal recess of the temporal horn

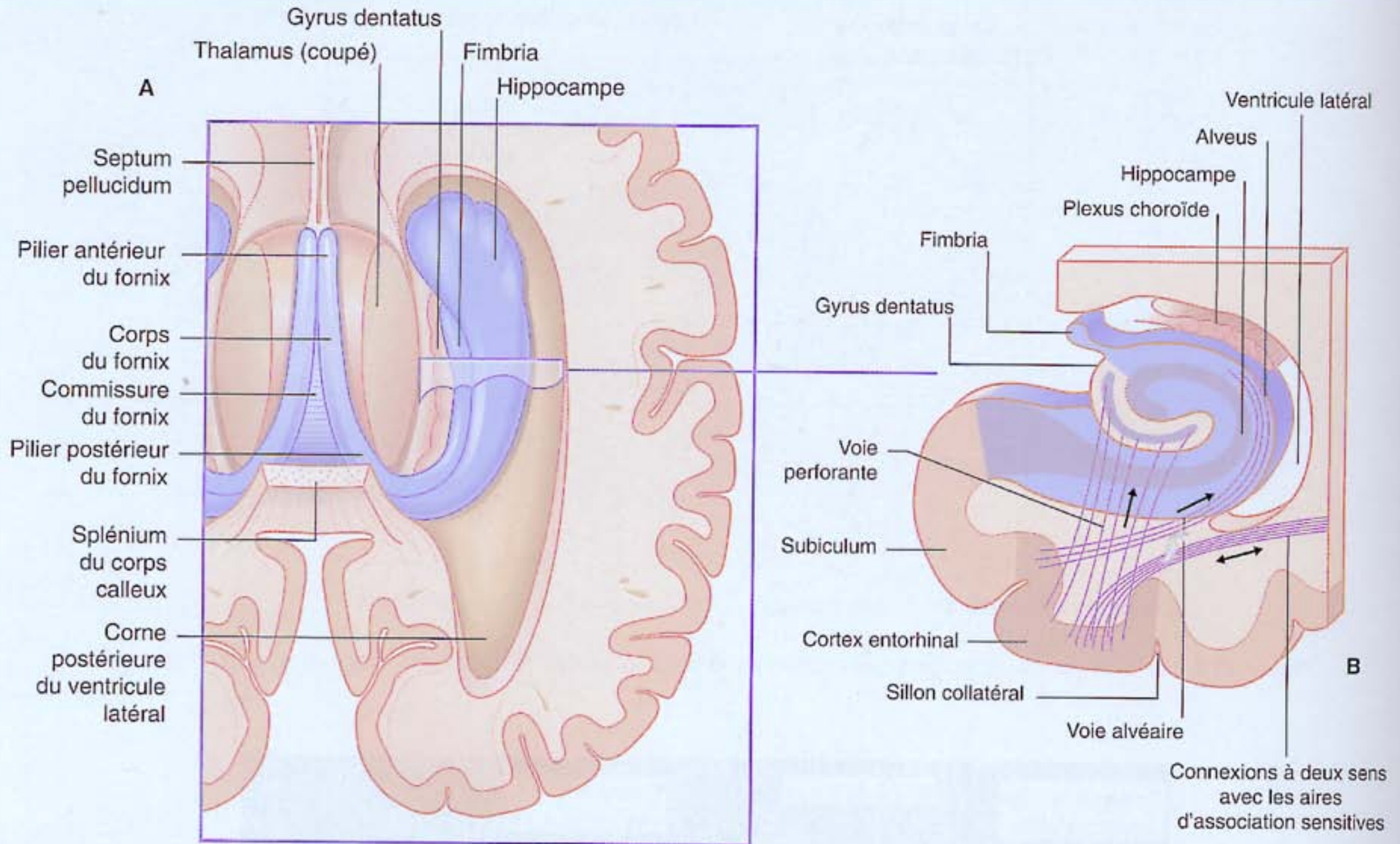
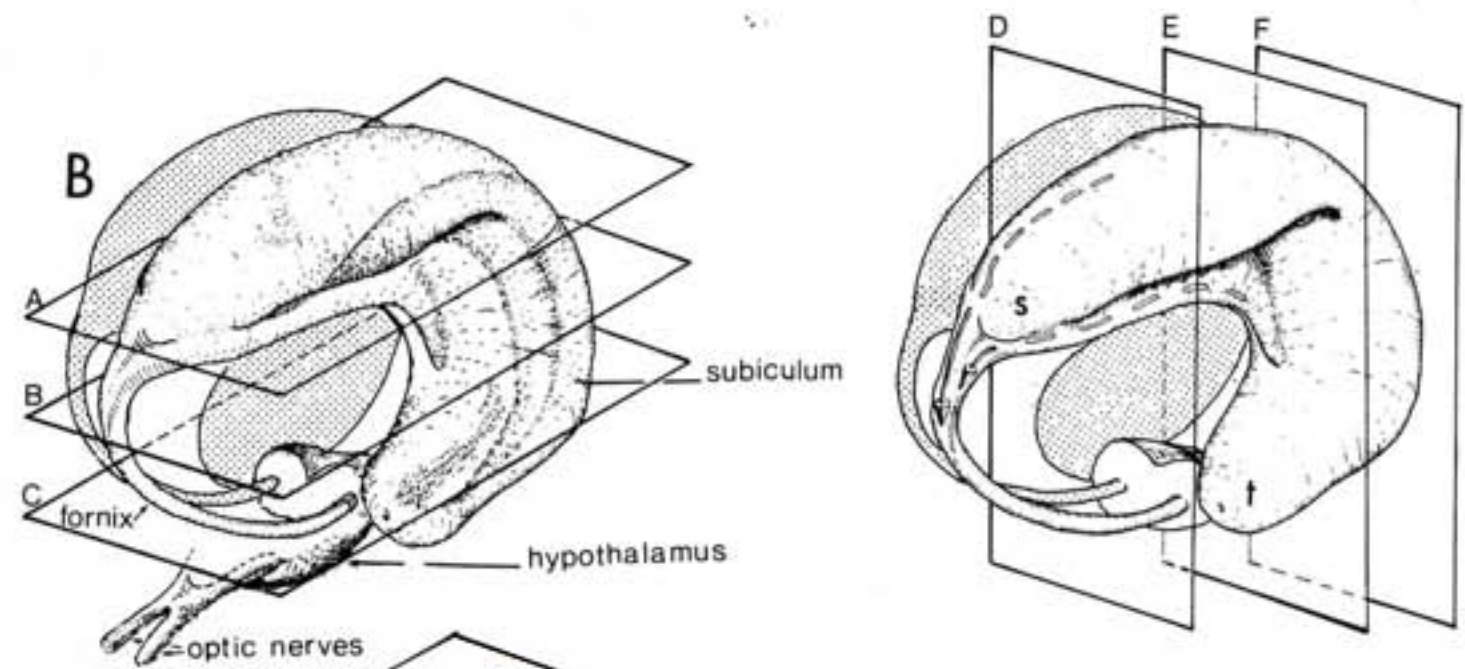
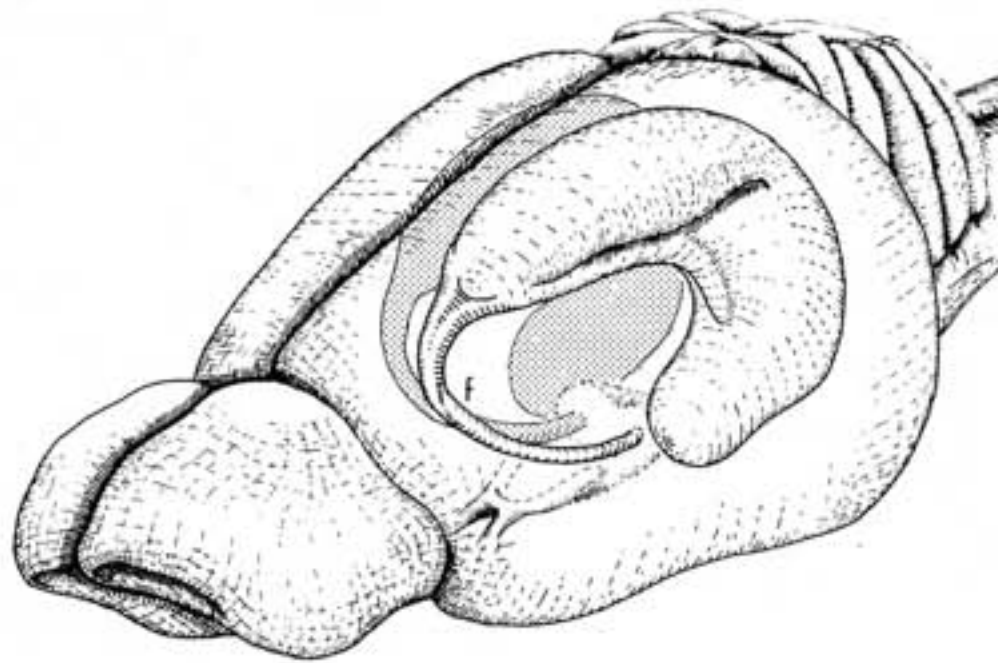
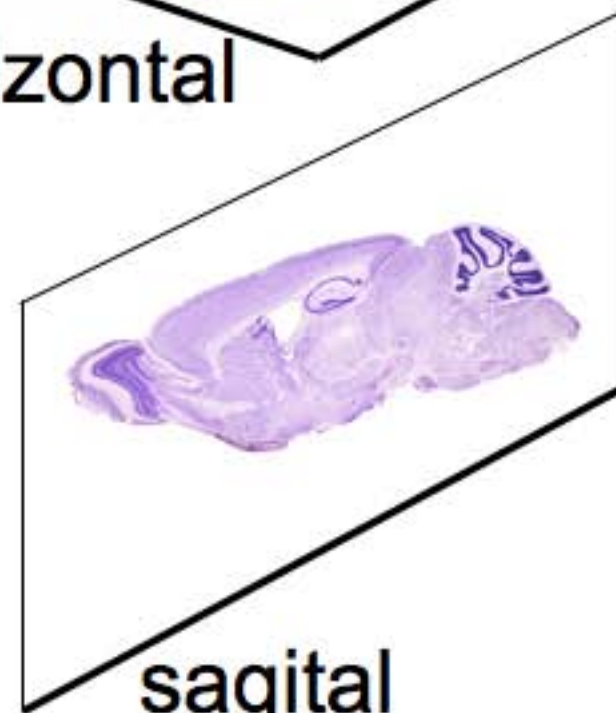
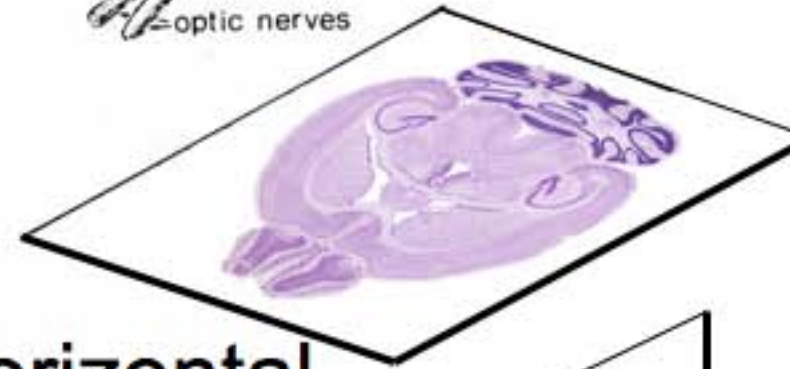


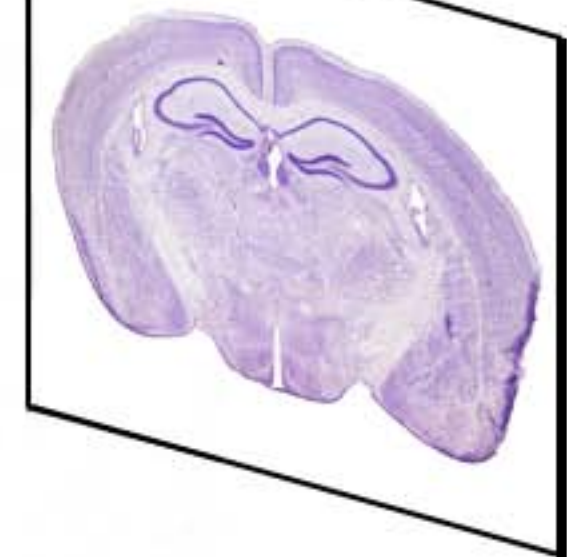
Figure 29.5 Formation hippocampique. **(A)** Vue par au-dessus. **(B)** Grossissement de A, montrant le cortex entorhinal et les trois parties composant la formation hippocampique.



horizontal



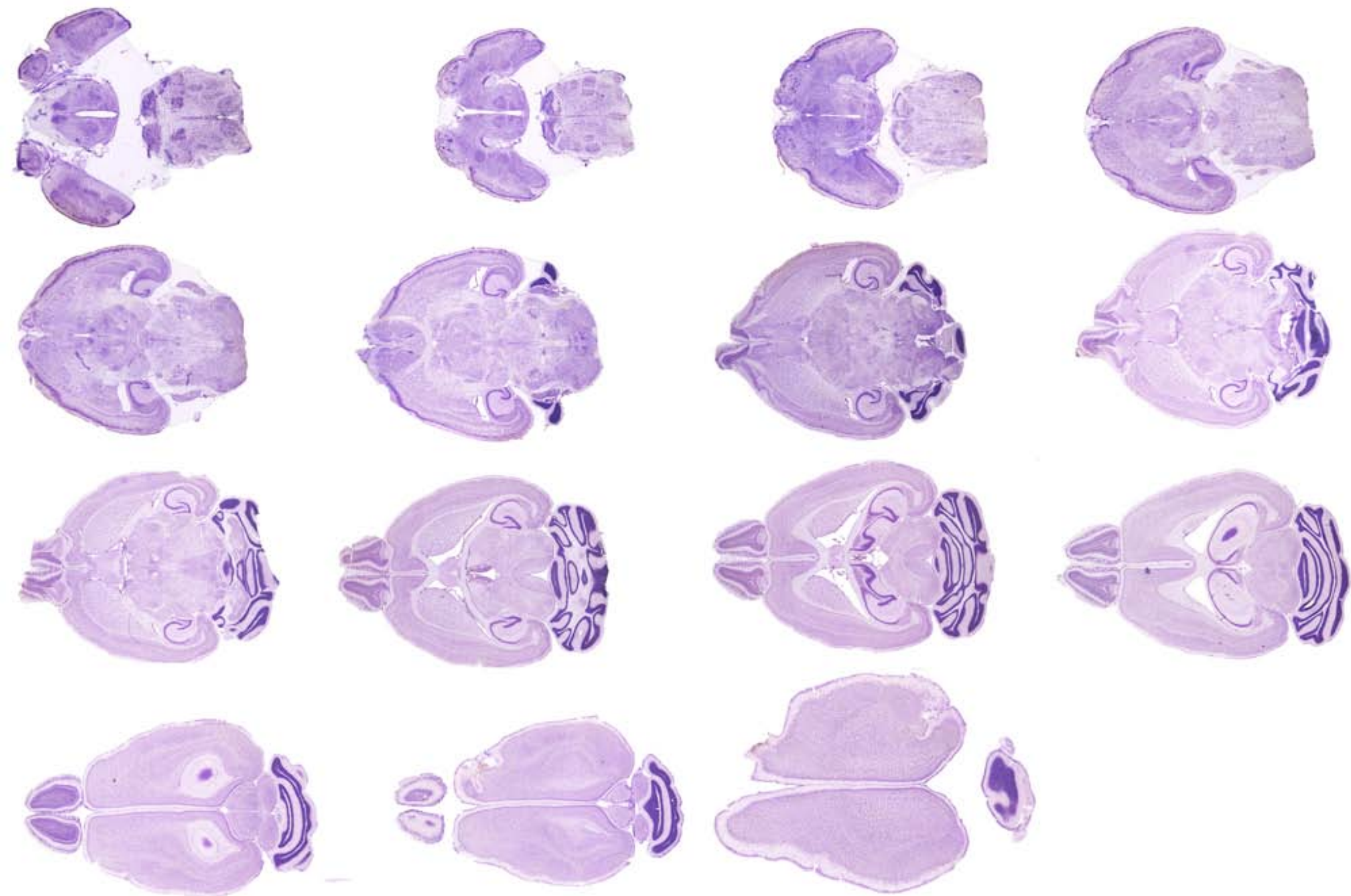
sagittal



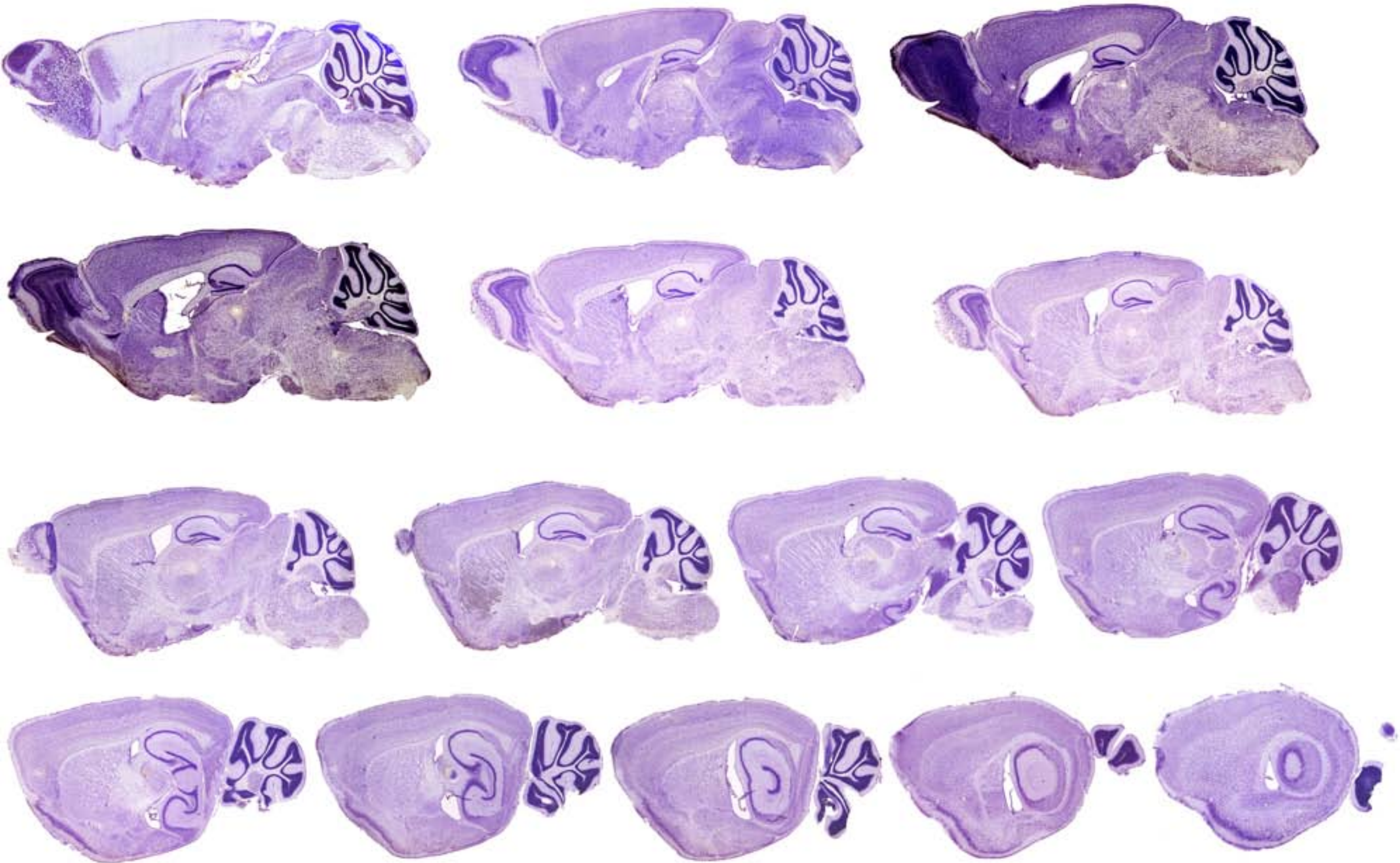
coronal

Hippocampal formation,
Amaral and Witter,
in The Rat Nervous System,
Edited by Paxinos, 2001

Horizontal view



Sagittal view



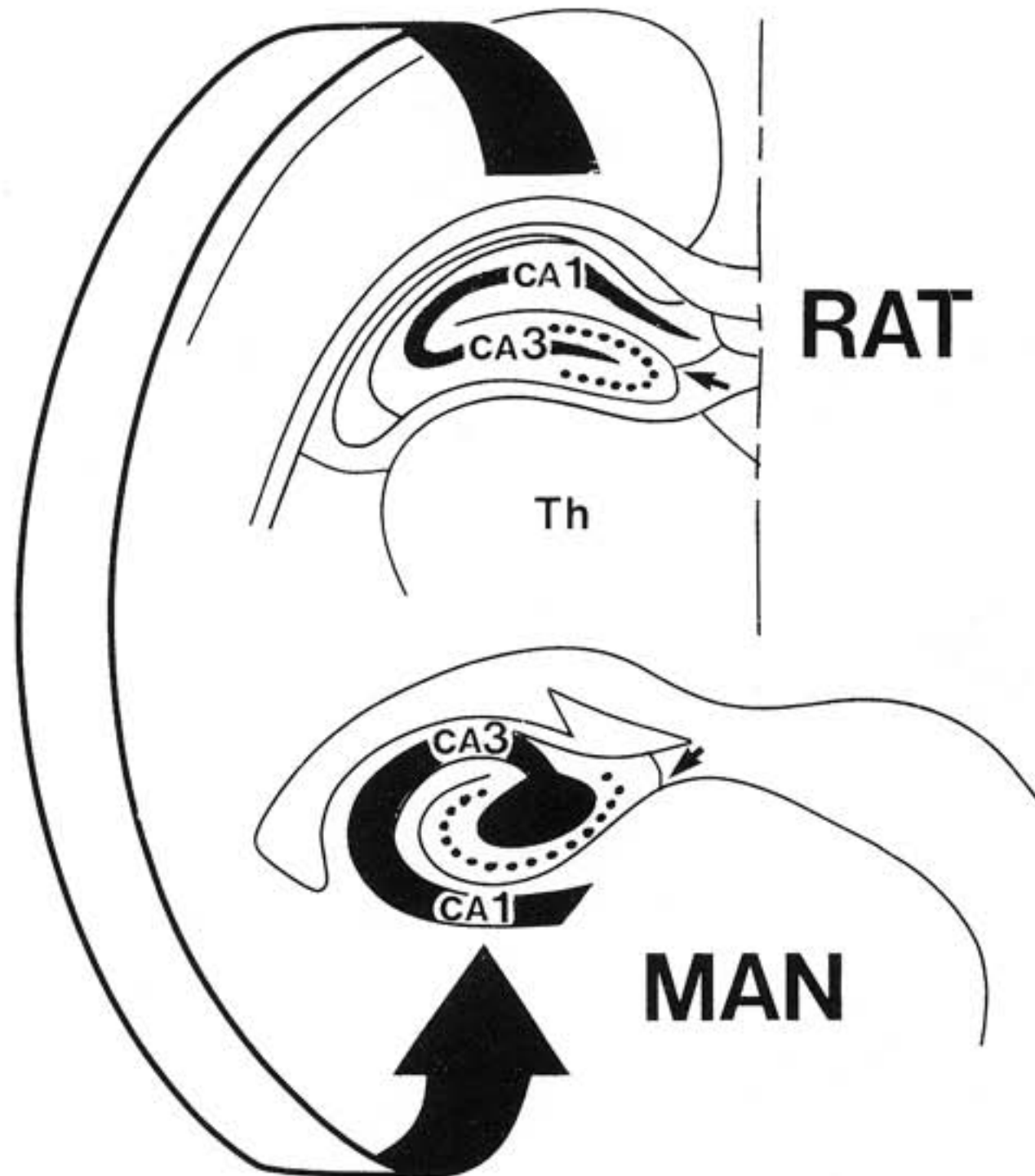
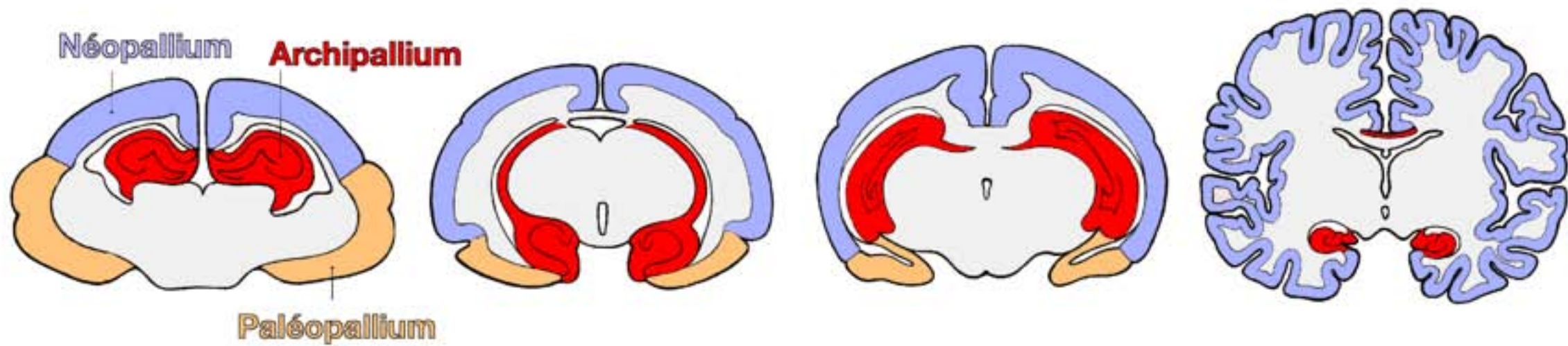


Fig. 6. Site of CA1 and CA3 in rats and humans (see p. 8).
Arrowheads show the hippocampal sulcus. The arrow indicates
the inversion of arrangements in the hippocampus in these
two species

CA1, superior region; CA3, inferior region; Th, thalamus

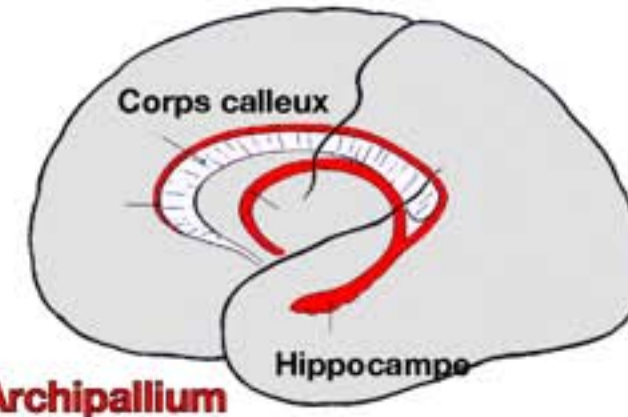
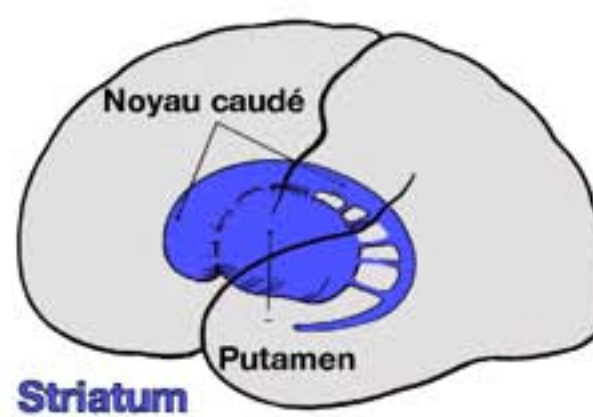
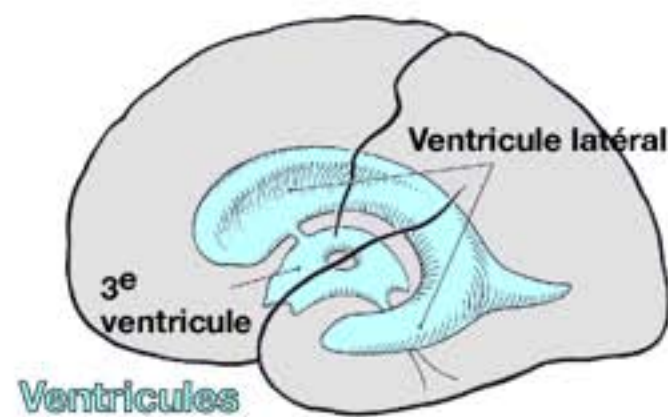
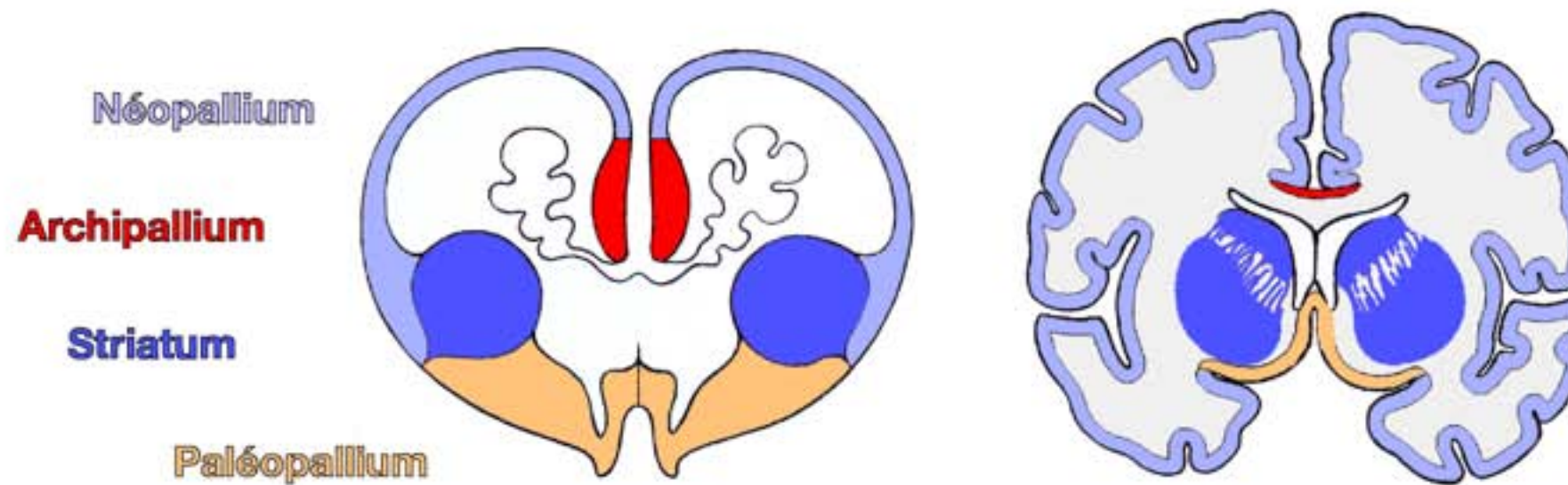


Mammifères primitifs
(type hérisson)

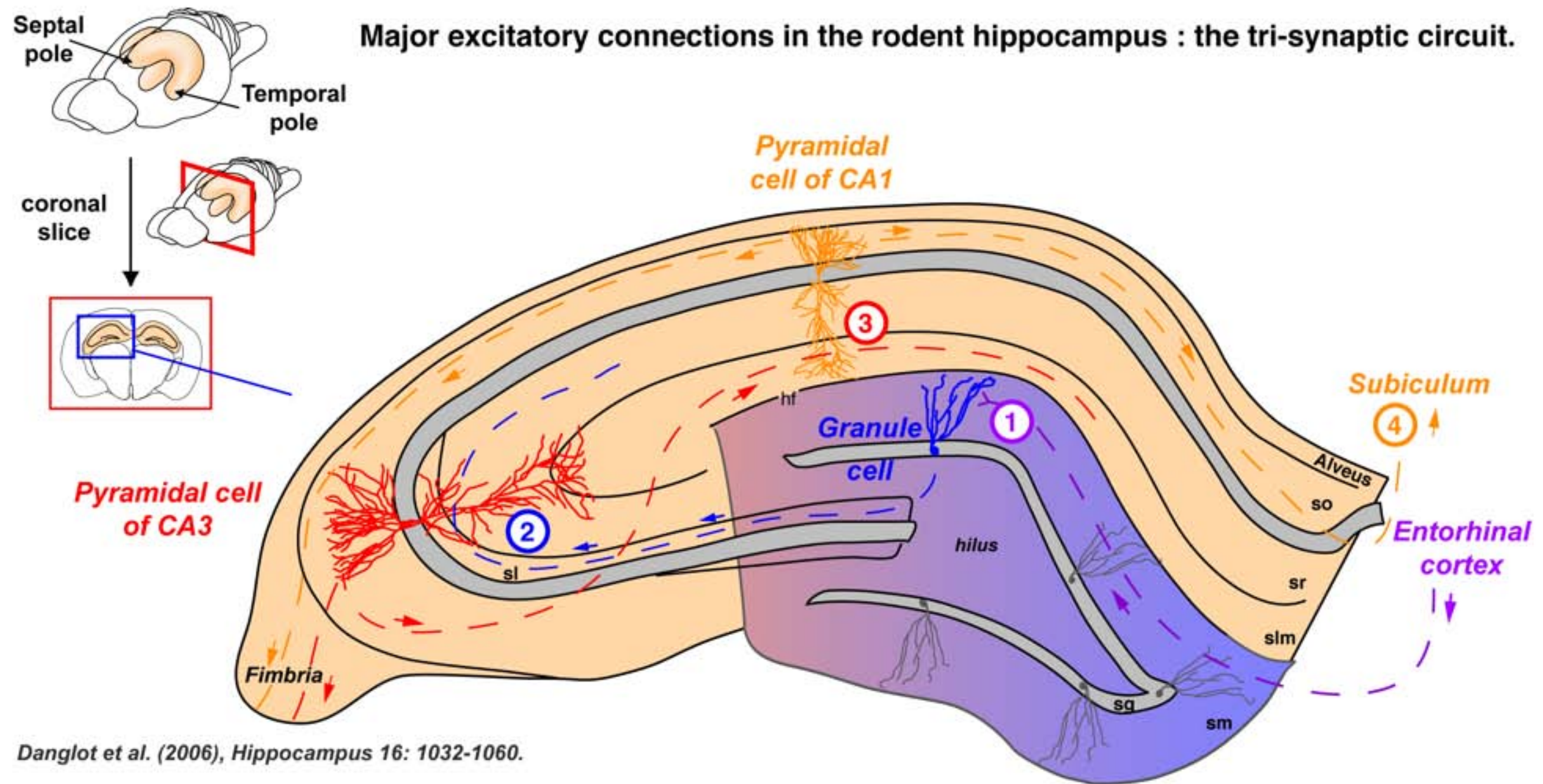
Primates primitifs
(type Tupaja)

Lémurien

Homme



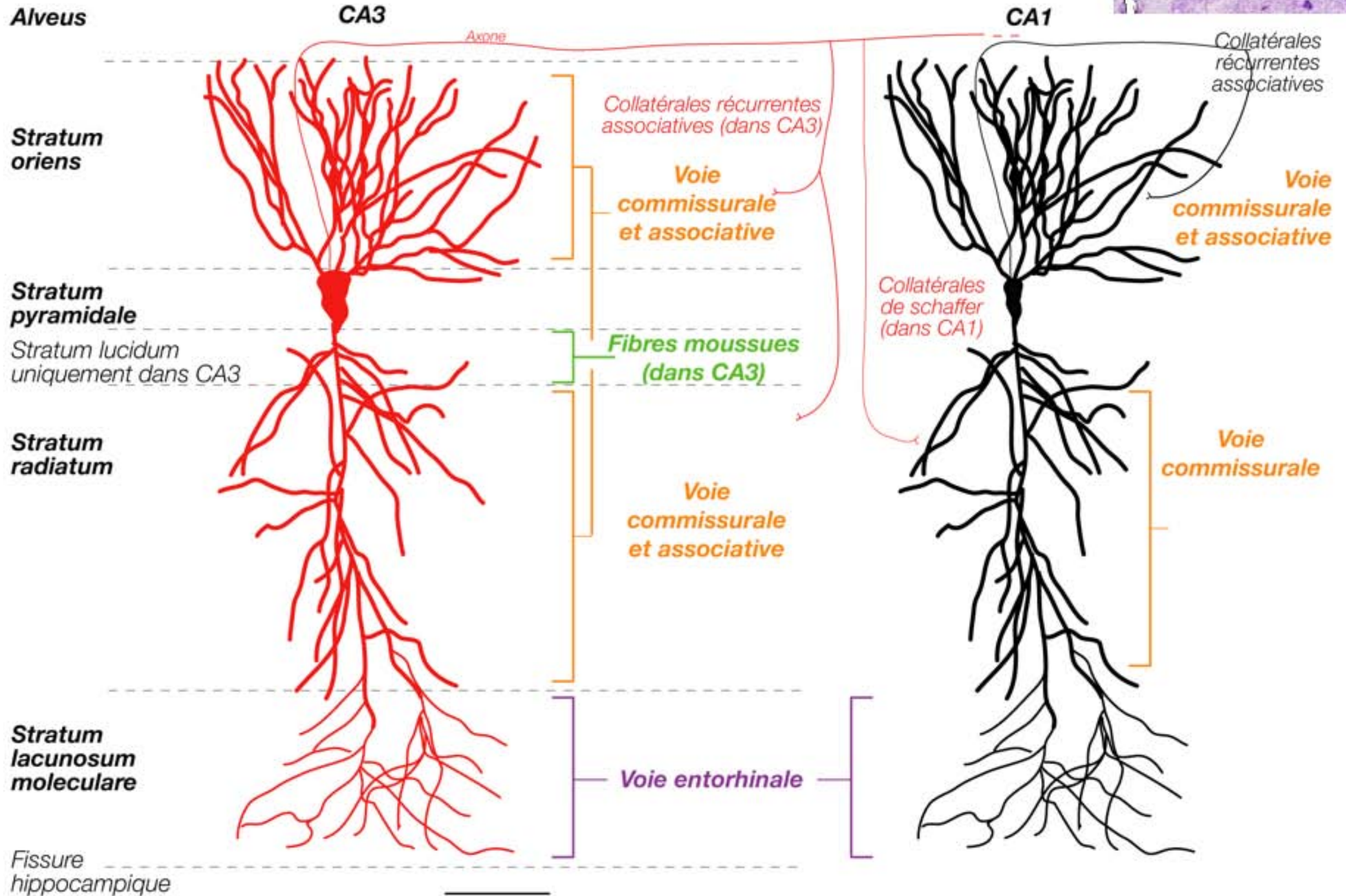
Major excitatory connections in the rodent hippocampus : the tri-synaptic circuit.

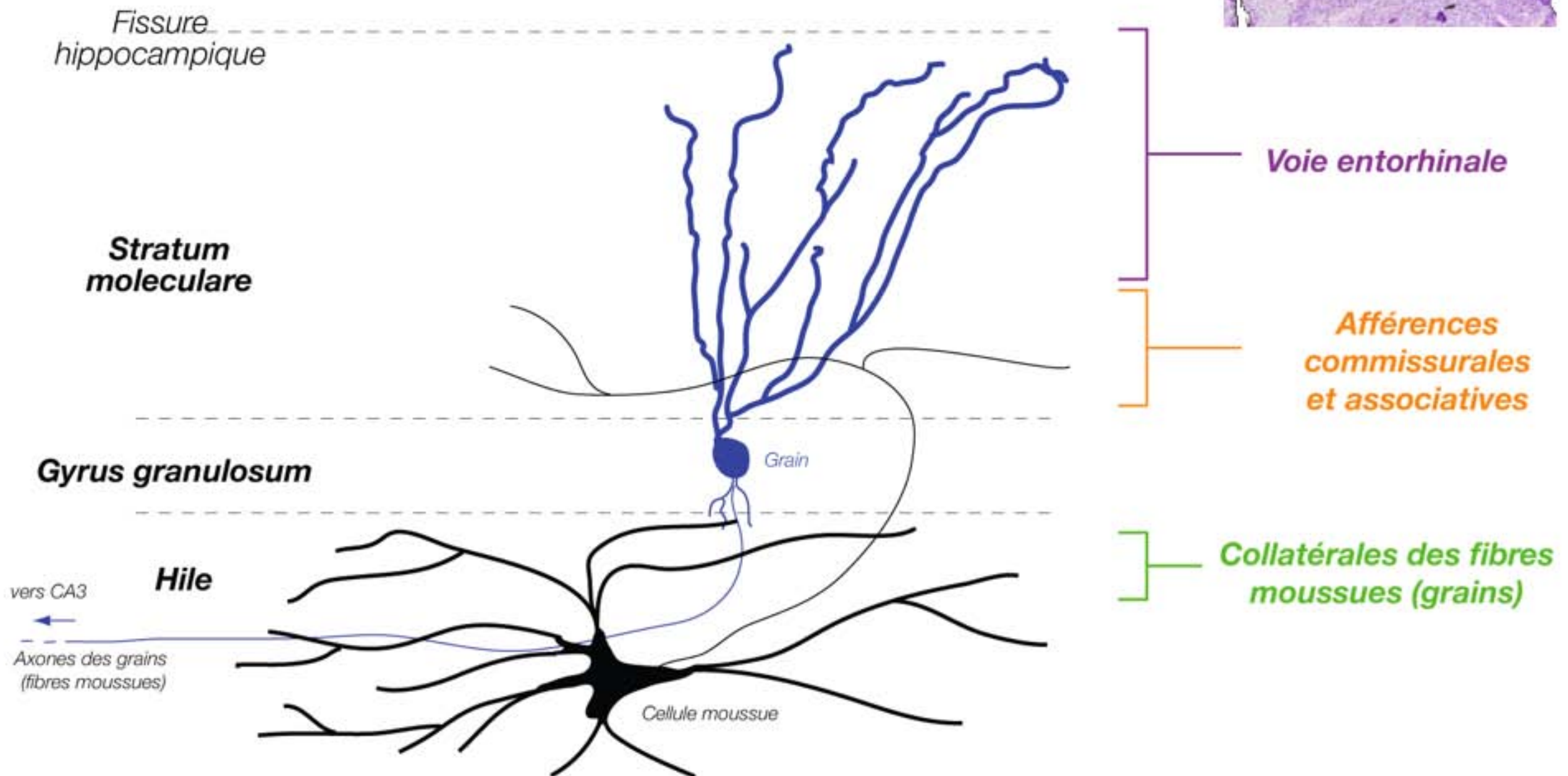


Danglot et al. (2006), *Hippocampus* 16: 1032-1060.

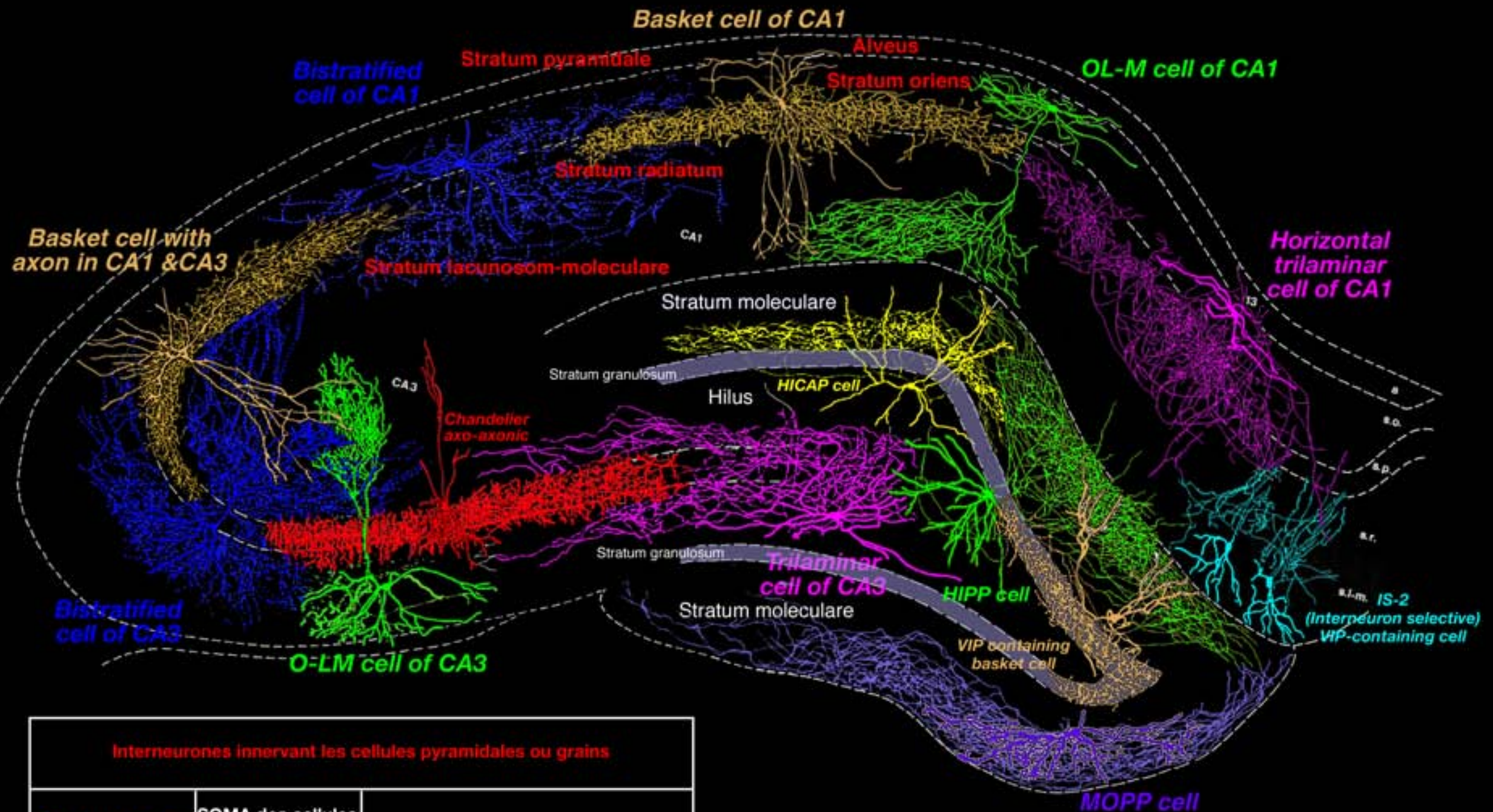
- - 1. Perforant path : axons from the entorhinal cortex innervate granule cells.
- - 2. The axons of the granule cells (mossy fibers) innervate pyramidal cells of CA3.
- - 3. The axons of the pyramidal cells of CA3 (Schaffer collaterals) innervate pyramidal cells of CA1.
- - 4. The axon of the pyramidal cells of CA1 innervate the subiculum and the entorhinal cortex.

Cells types





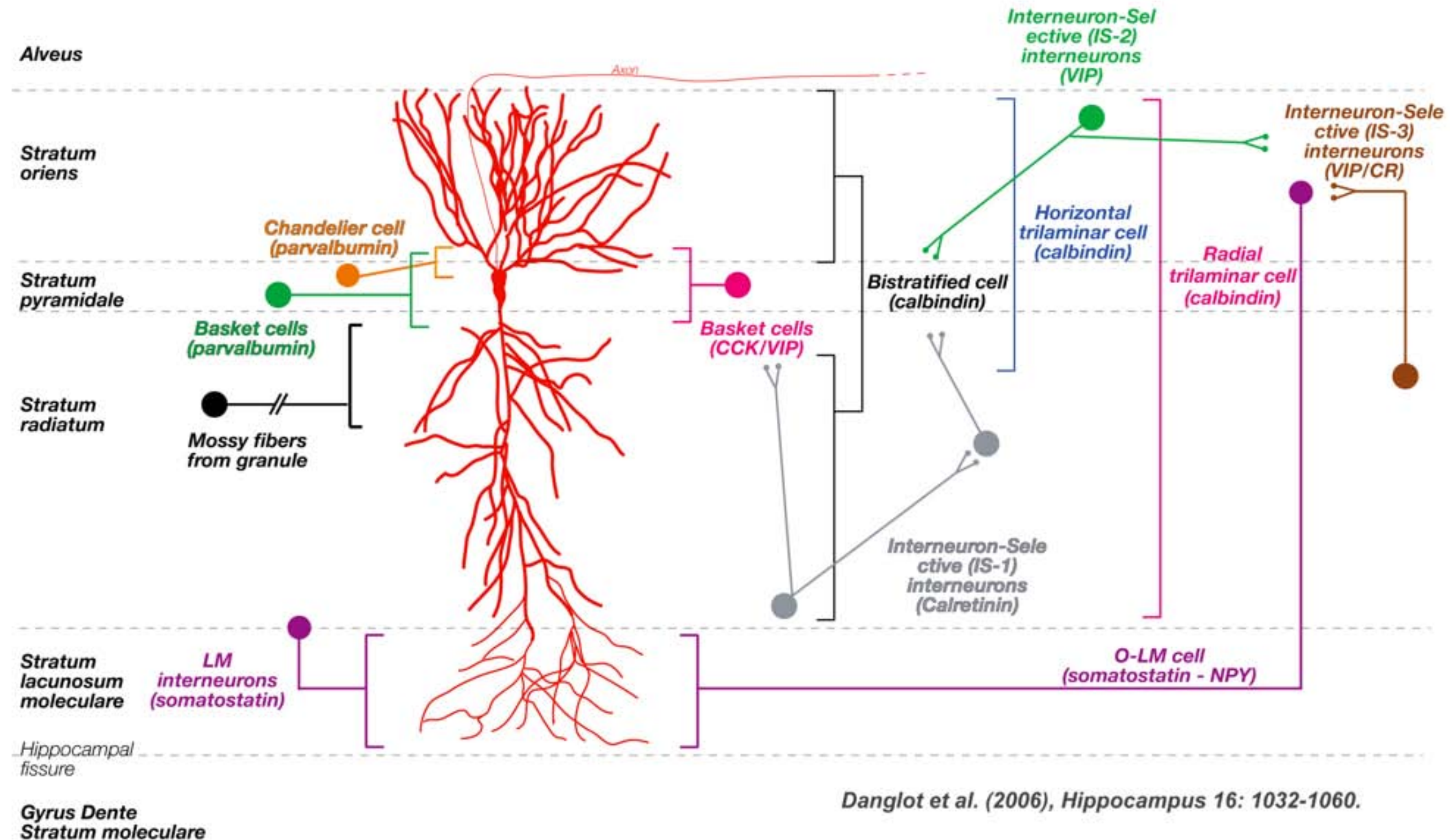
Classification des interneurones hippocampiques



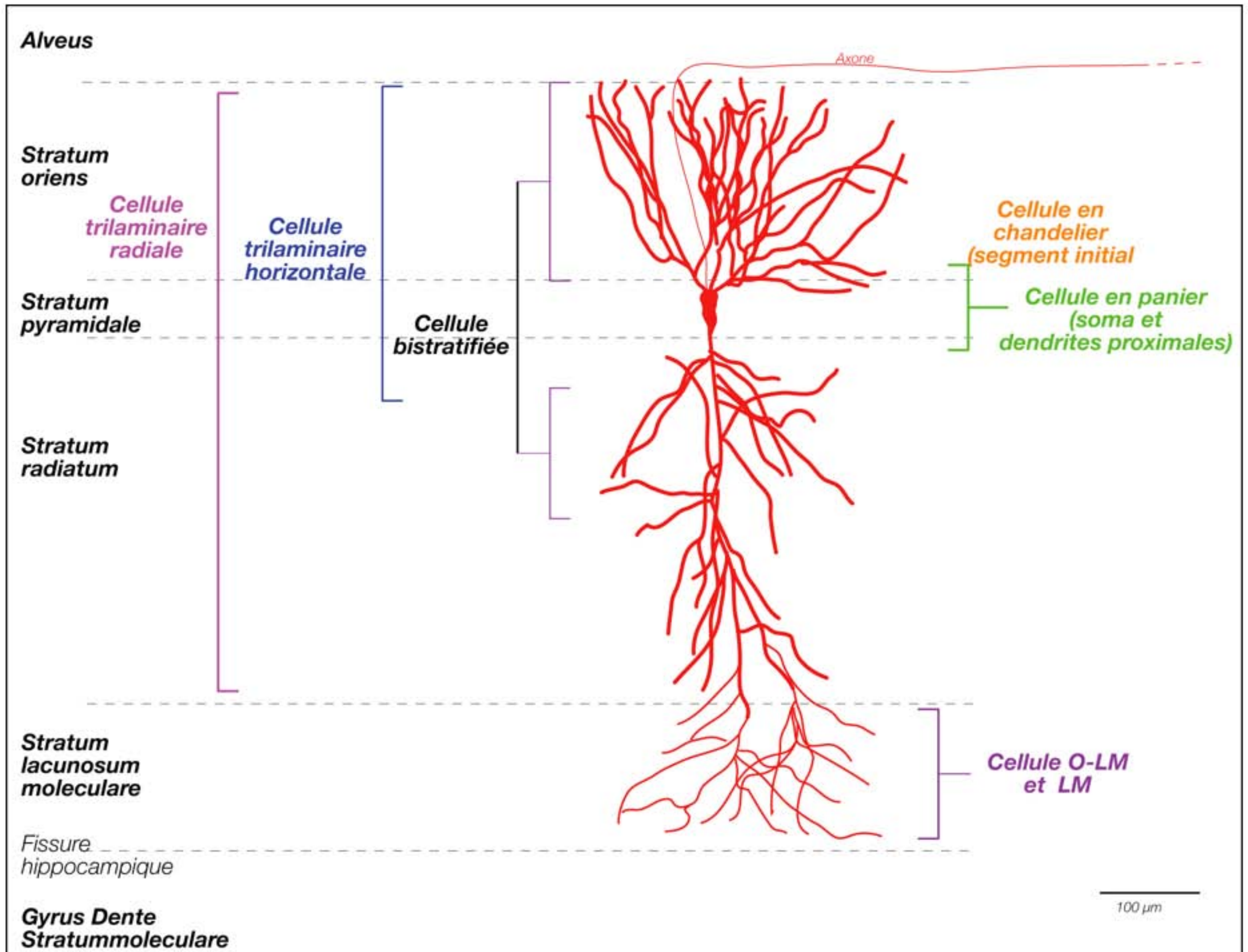
Interneurones innervant les cellules pyramidales ou grains		
Cellule en panier	SOMA des cellules excitatrices	Parvalbumine
Chandelier	Segment initial de l'axone	
Bistratifiée Trilaminaire HICAP MOPP	Dendrites proximales (sr et so)	Calbindine
O-LM LM HIPP	Dendrites distales (slm)	Somatostatine, NPY

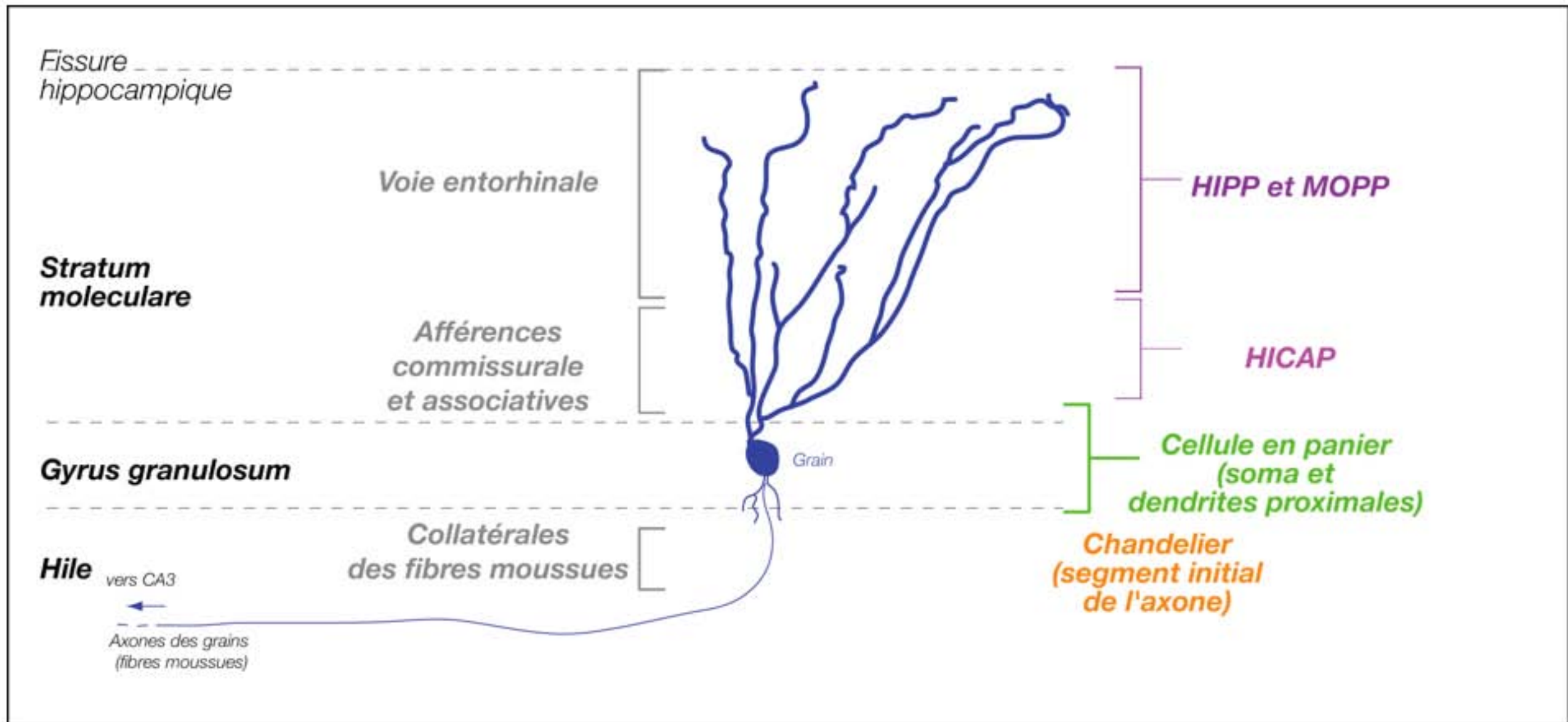
Interneurones innervant les interneurones		
IS-1, IS-2, IS-3	Dendrites	Calrétinine

GABAergic afferences on hippocampal pyramidal cells.

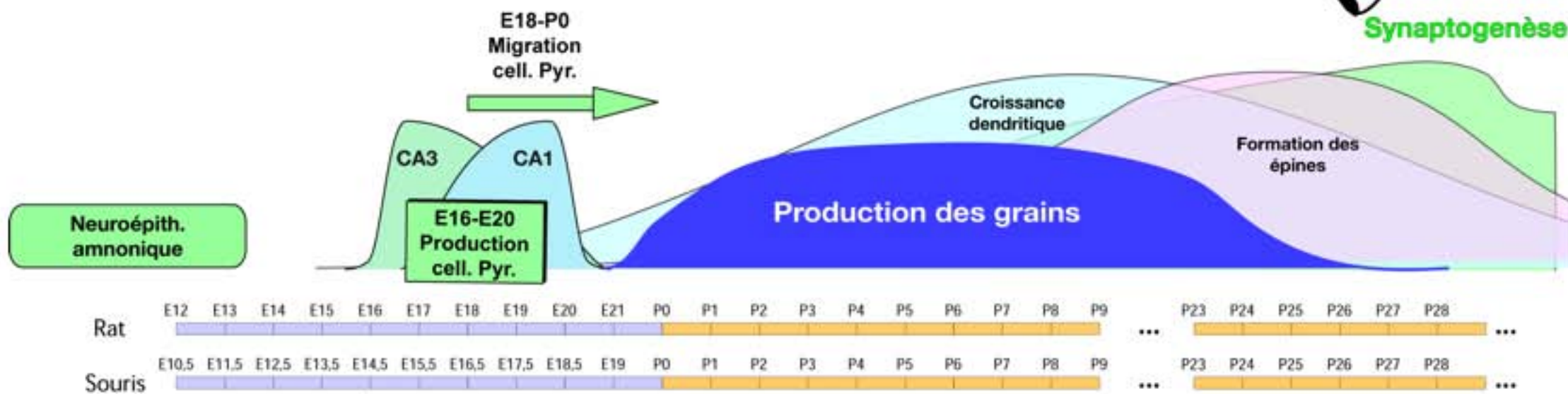
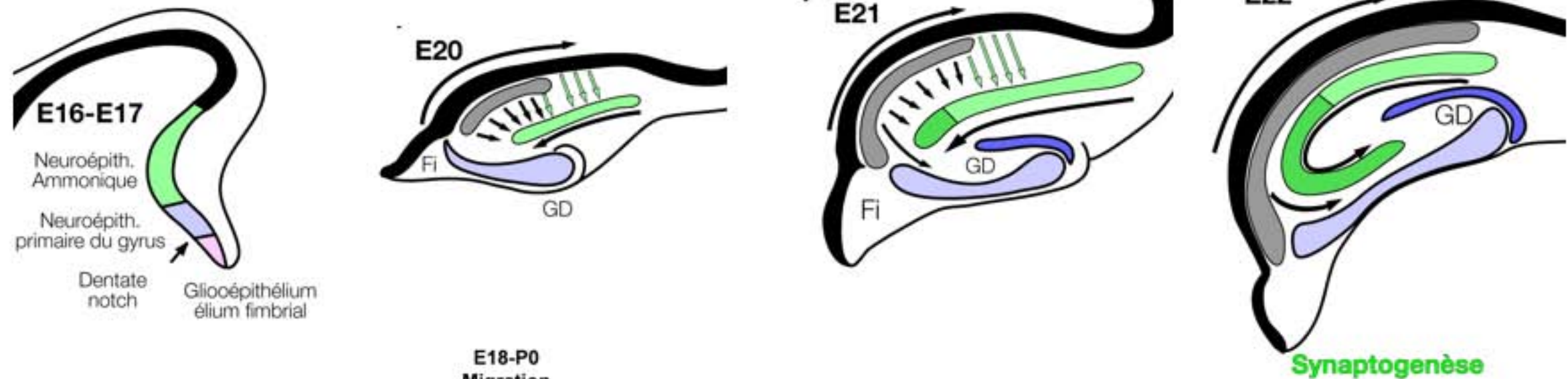


Danglot et al. (2006), *Hippocampus* 16: 1032-1060.

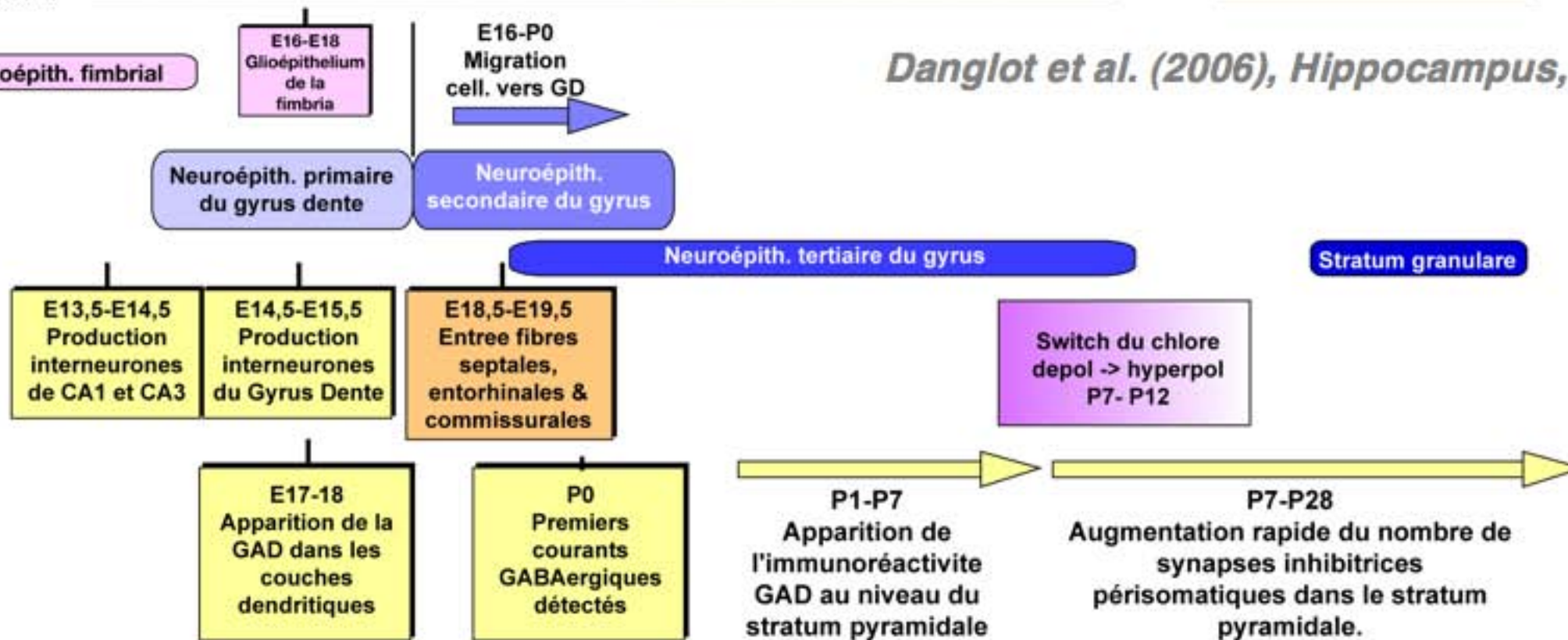




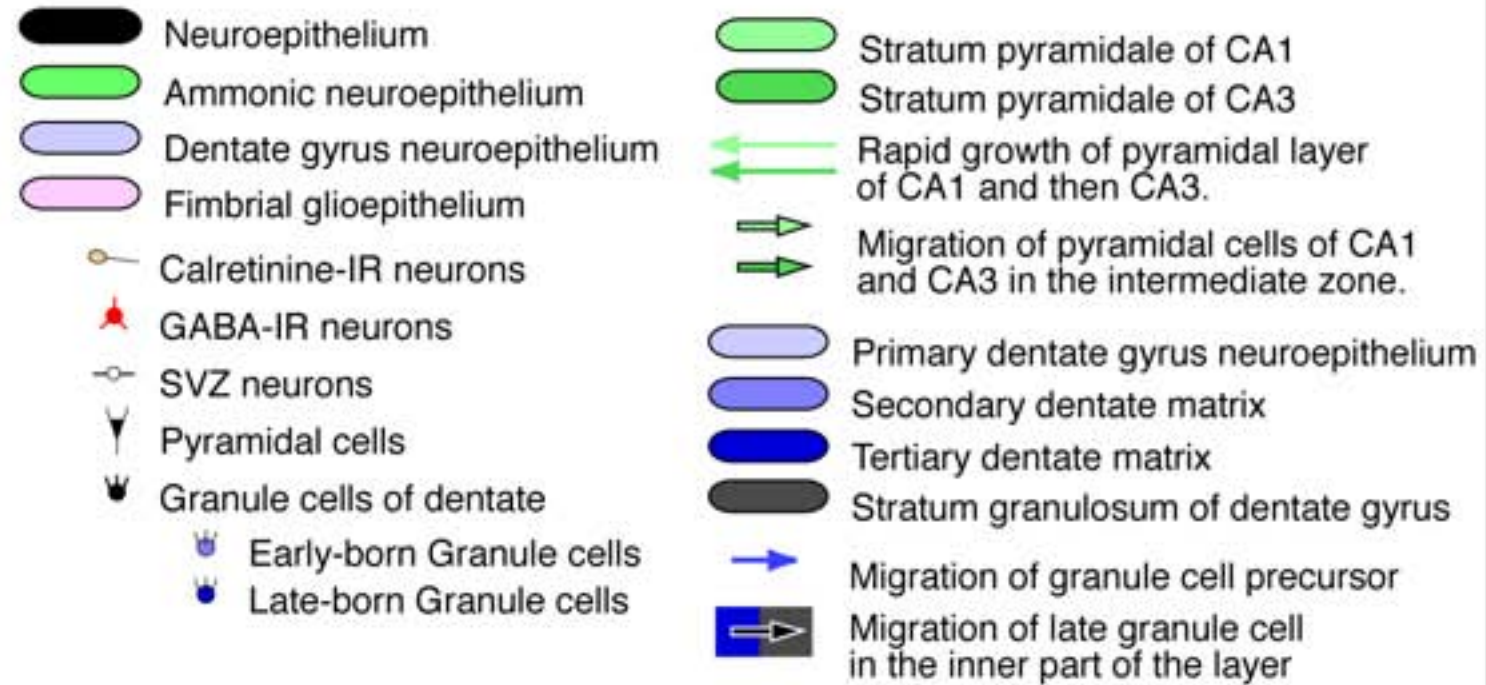
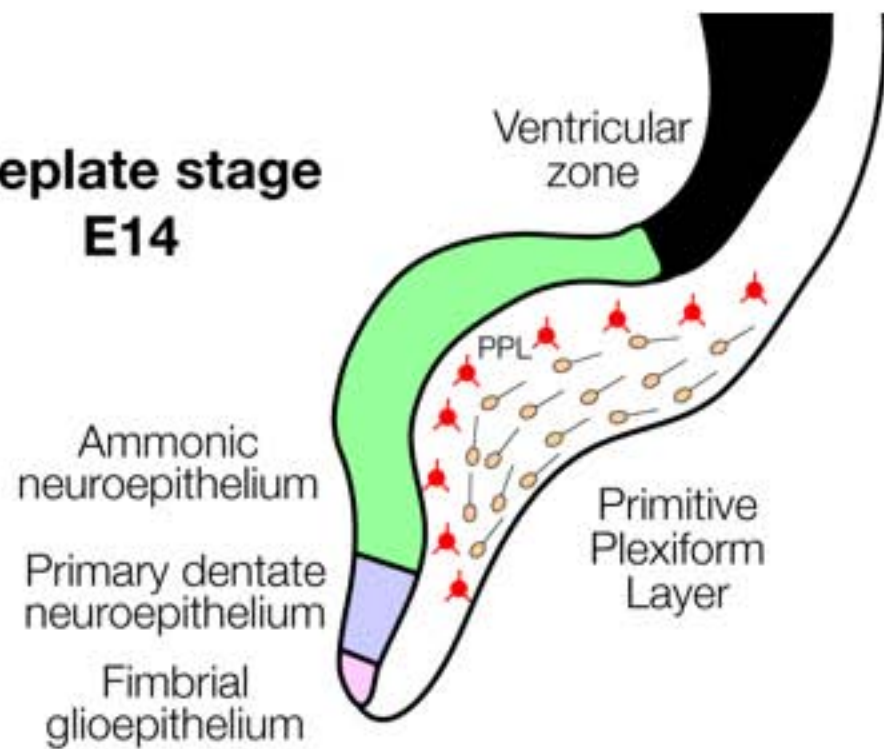
Development of the hippocampus & Cell migration



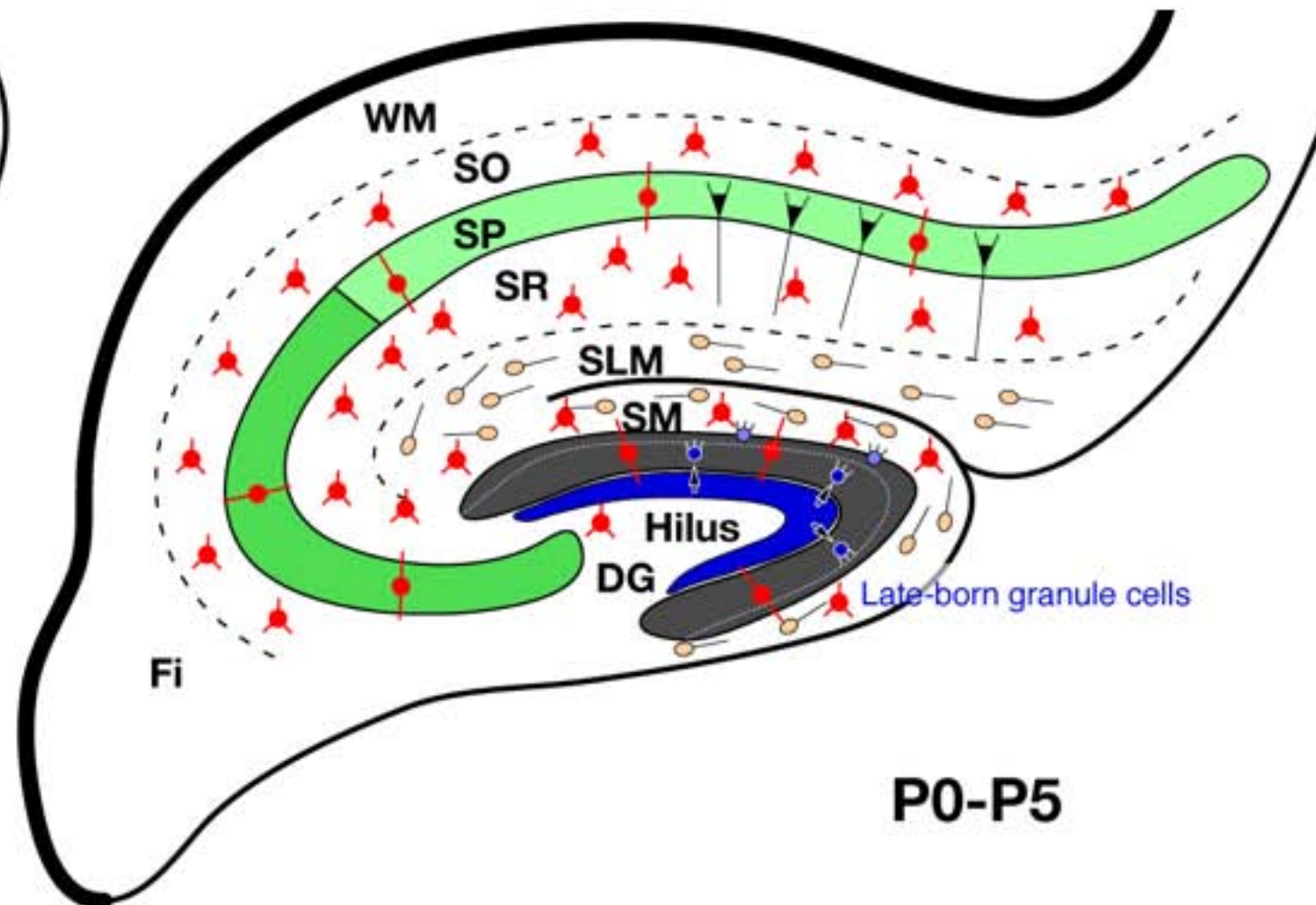
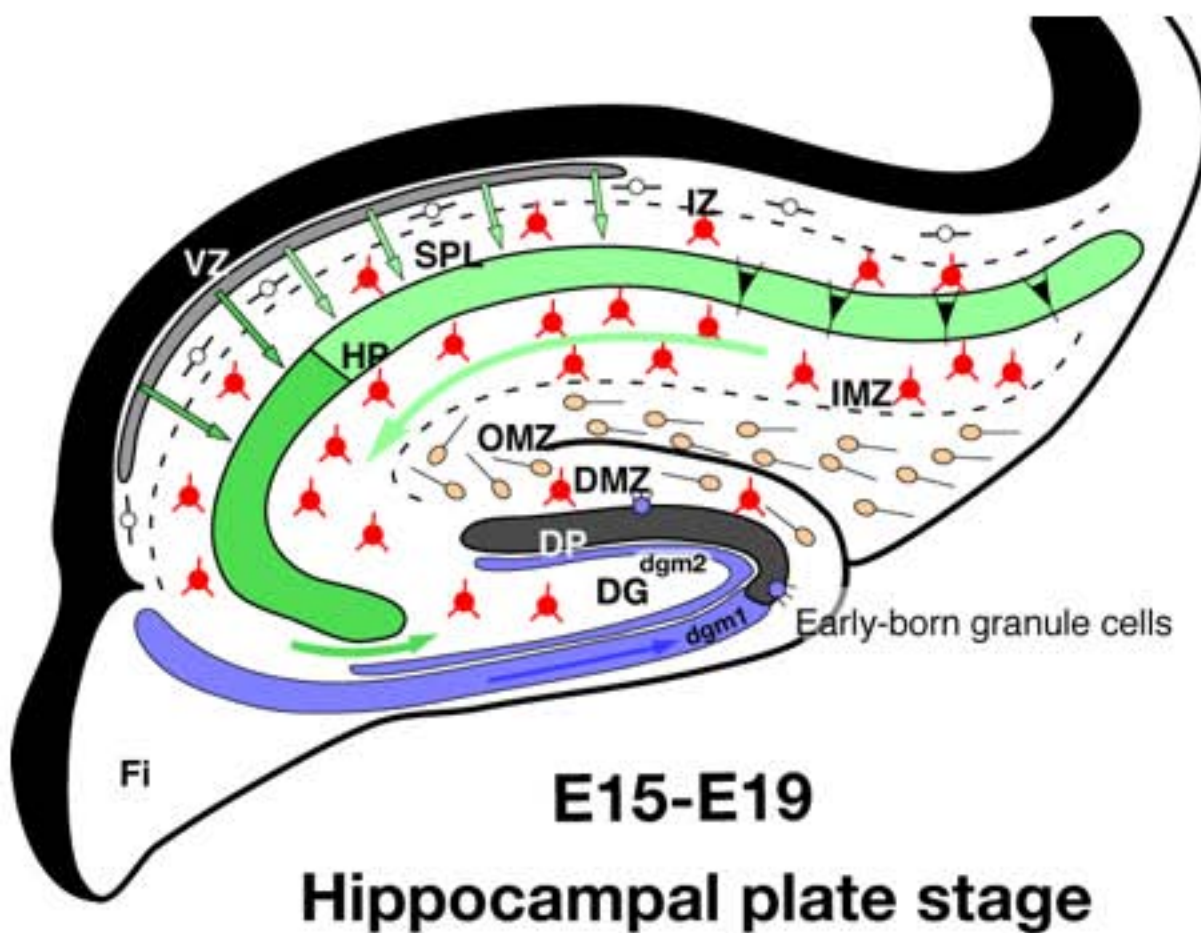
Danglot et al. (2006), *Hippocampus*, 16: 1032-1060.



Preplate stage E14

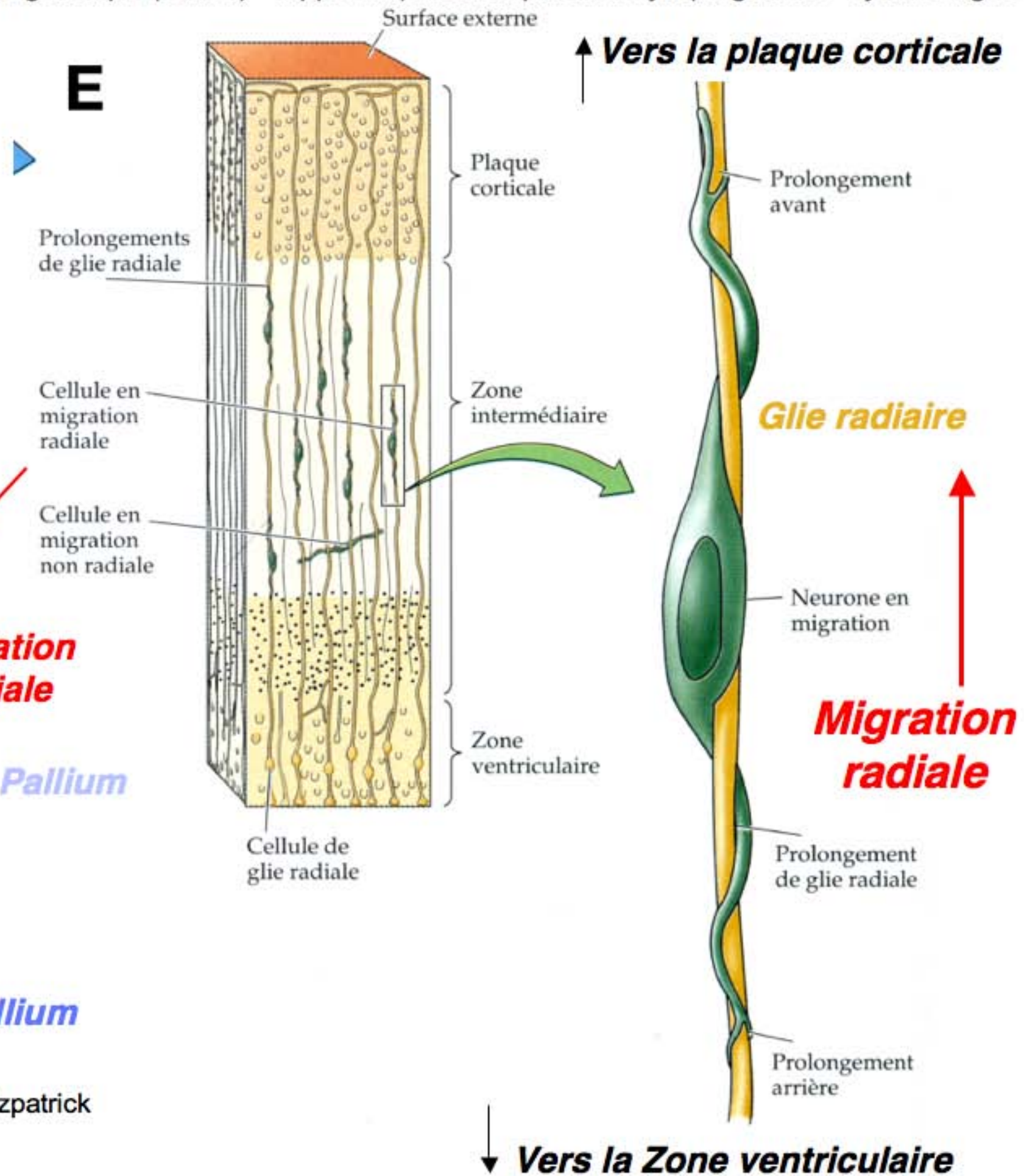
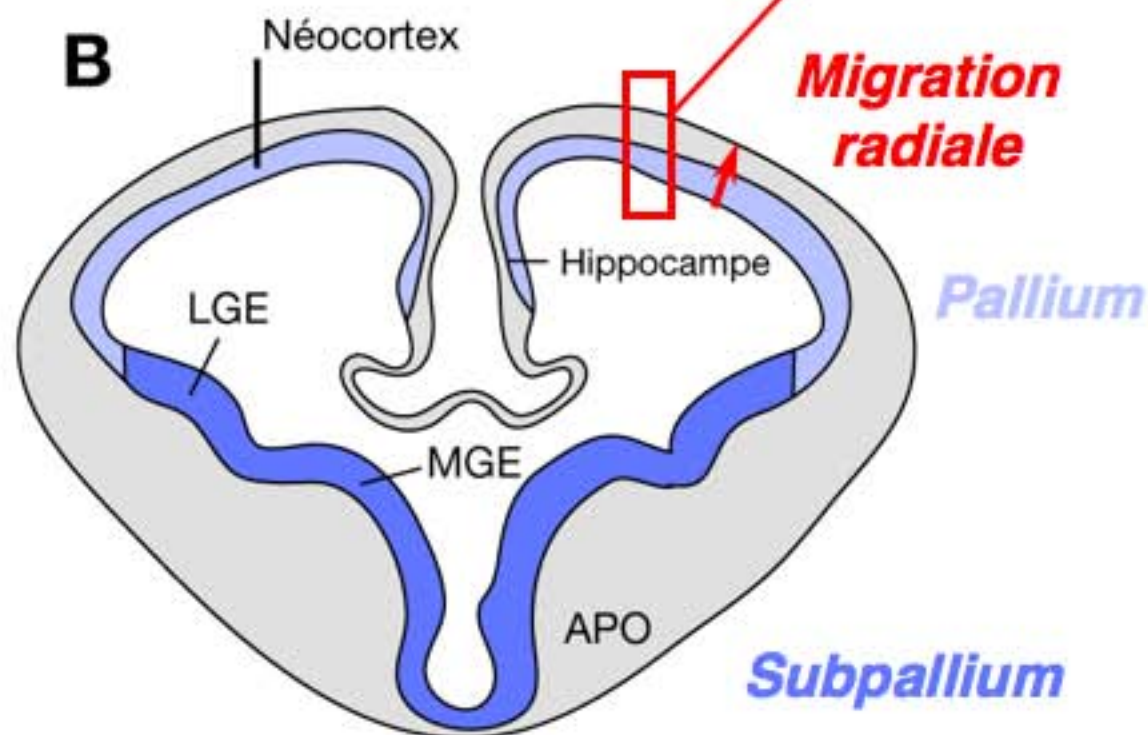
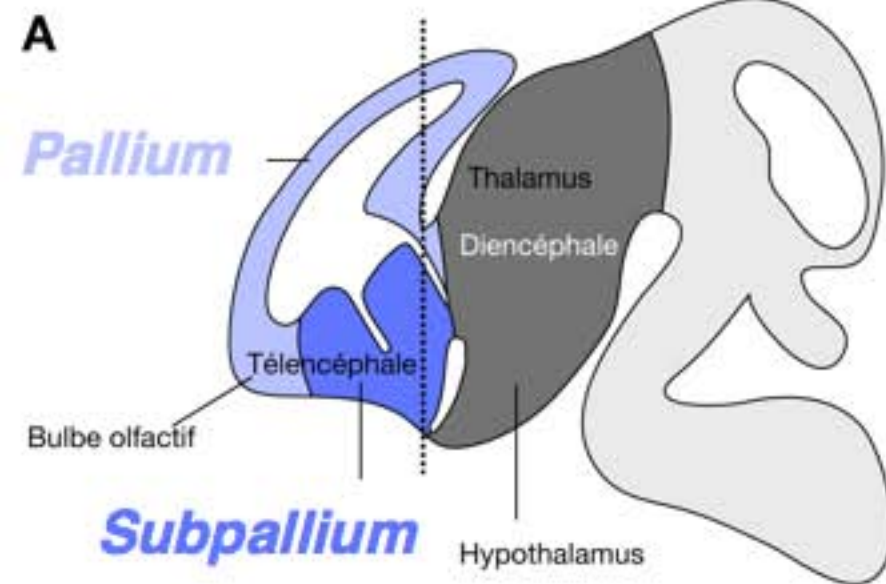


Danglot et al. (2006), Hippocampus, 16: 1032-1060.

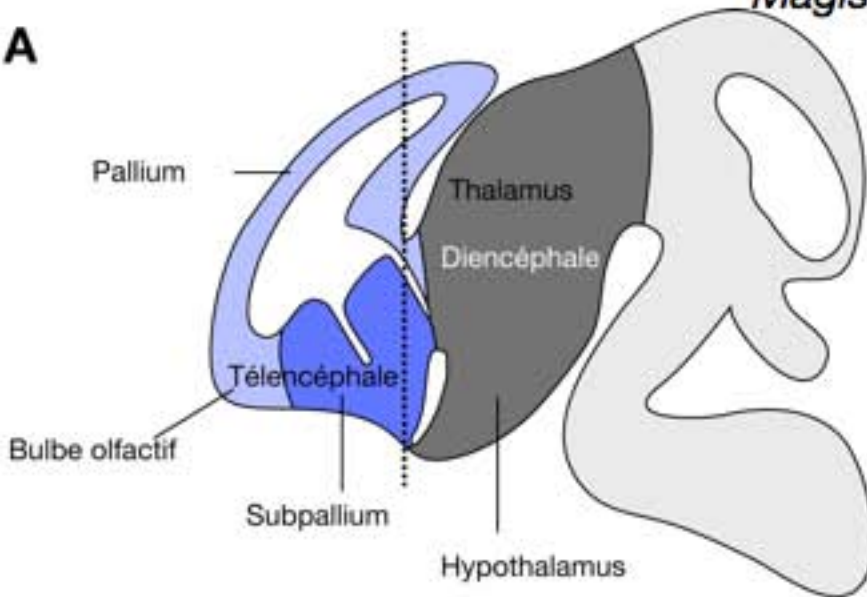


Modes of migration of excitatory cells

Télencéphale



A

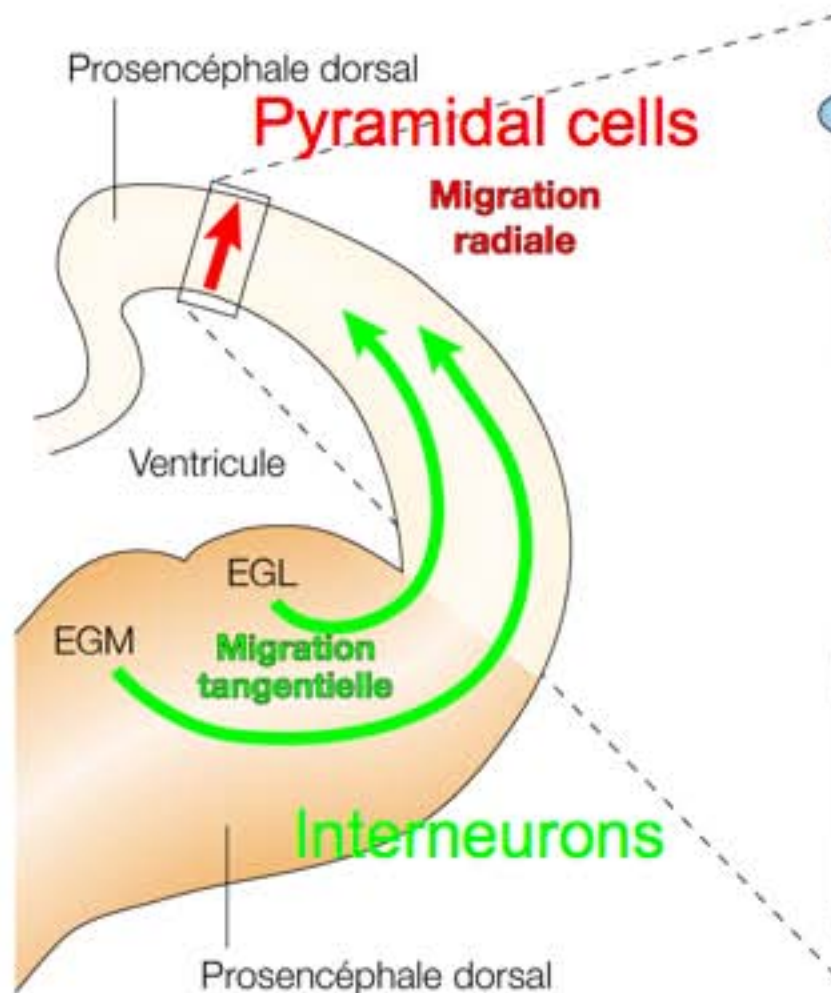


Nature Reviews Neuroscience 3, 423-432 (June 2002)

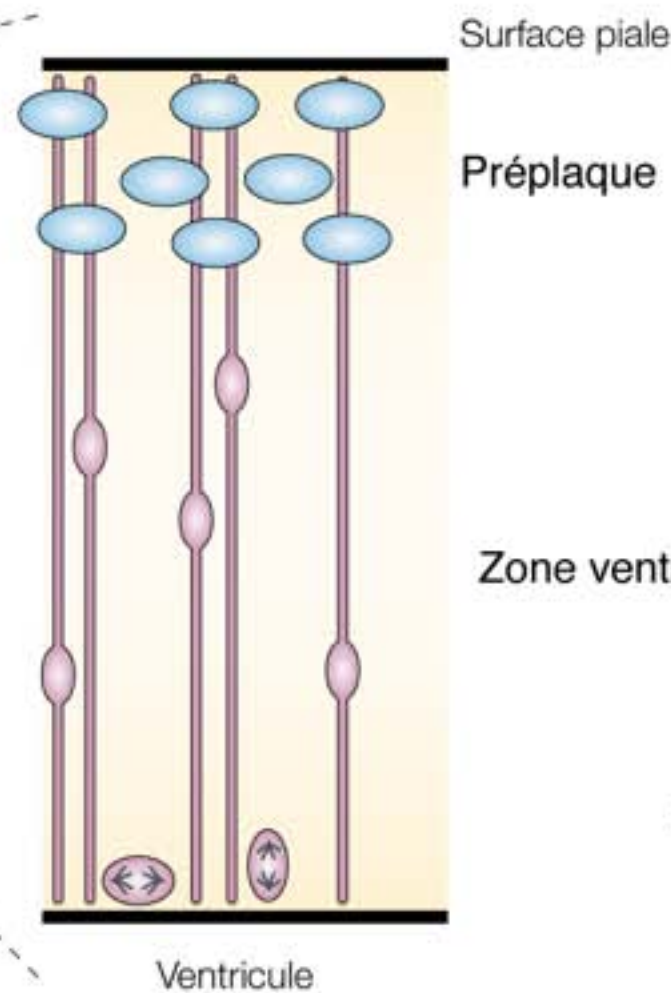
Modes of neuronal migration in the developing cerebral cortex

Bagirathy Nadarajah & John G. Parnavelas

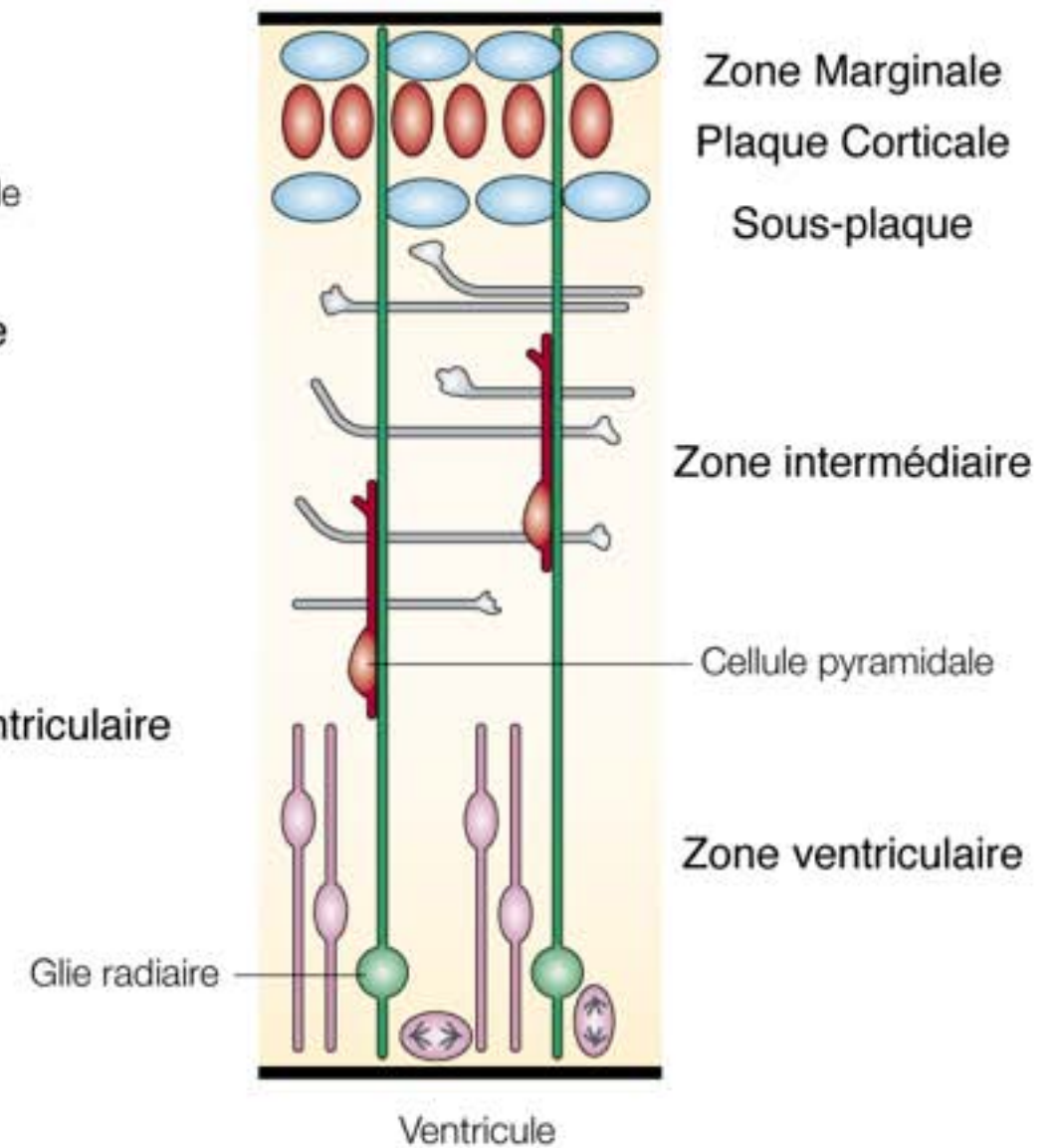
C



Prosencéphale en développement

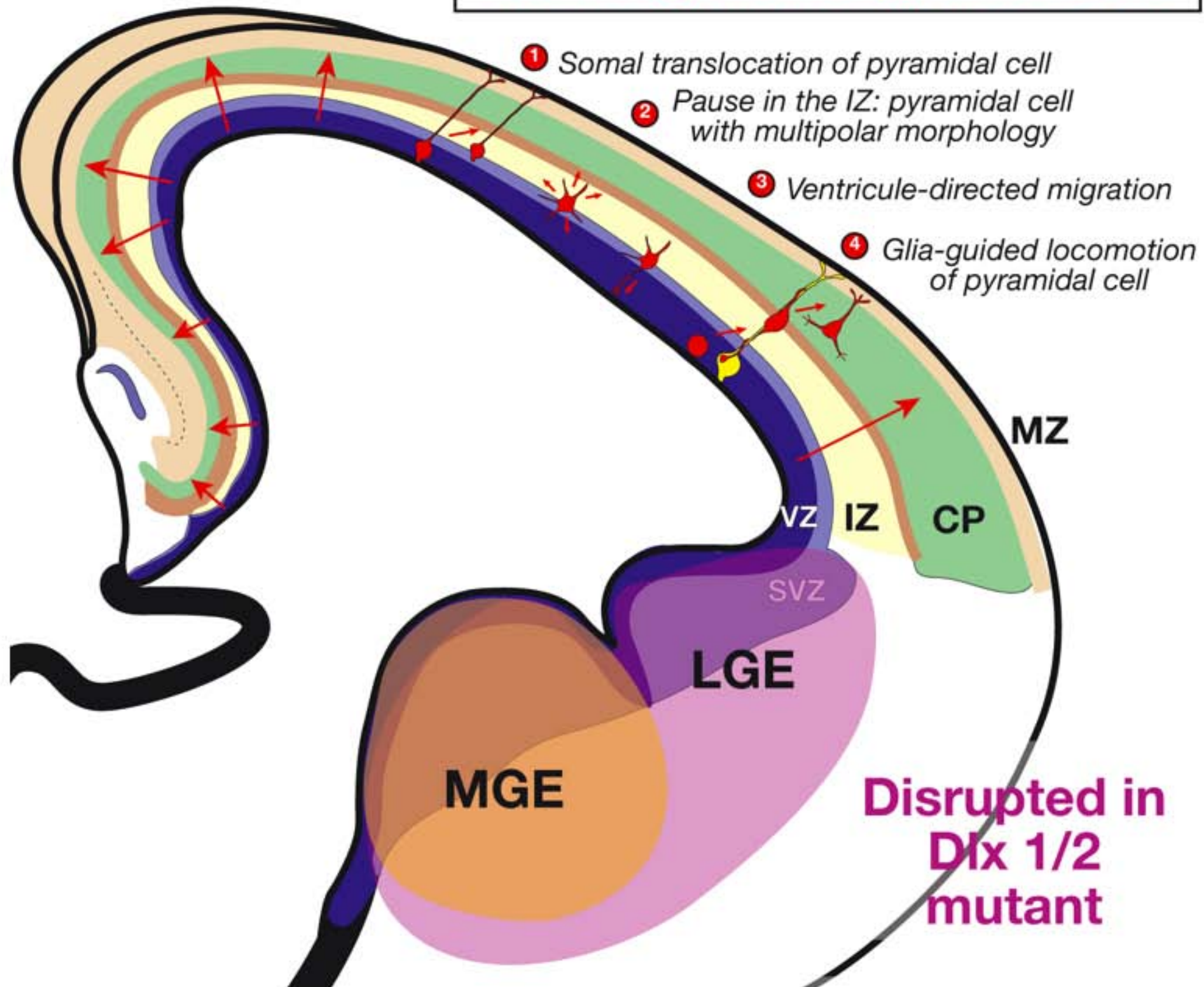


Stade de la préplaque



Stade de la plaque corticale

Radial migration of pyramidal cells



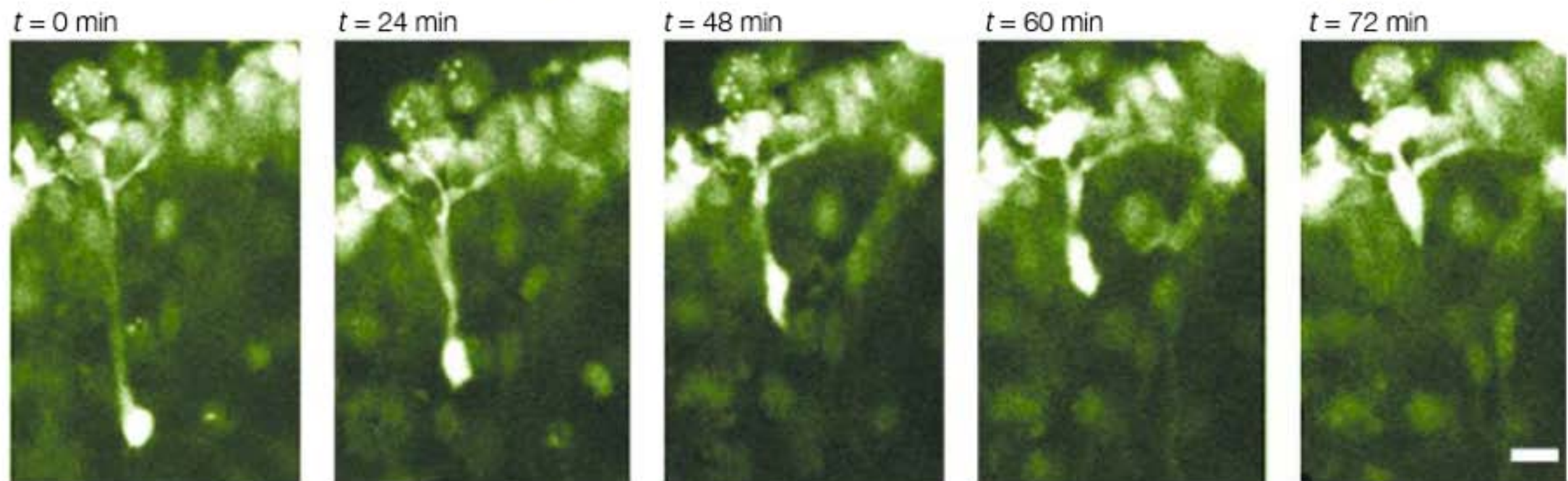


Figure 3 | **Somal translocation.** Time-lapse images of a cell showing somal translocation in a mouse cortical slice that was labelled with Oregon Green BAPTA-1 488 AM. Images were acquired every minute and each frame shows a single optical section. Scale bar, 10 μ m. See [Supplementary Movie](#) from REF. 31 © 2001 Macmillan Magazines Ltd.

Nadarajah & Parnavelas
Nat Rev Neur (2002)vol.3:423.

Somal translocation

E16
Terminal
Translocation
Total recording time:
300 min.

Nadarajah, Nature Neurosci. 4, 143–150 (2001).

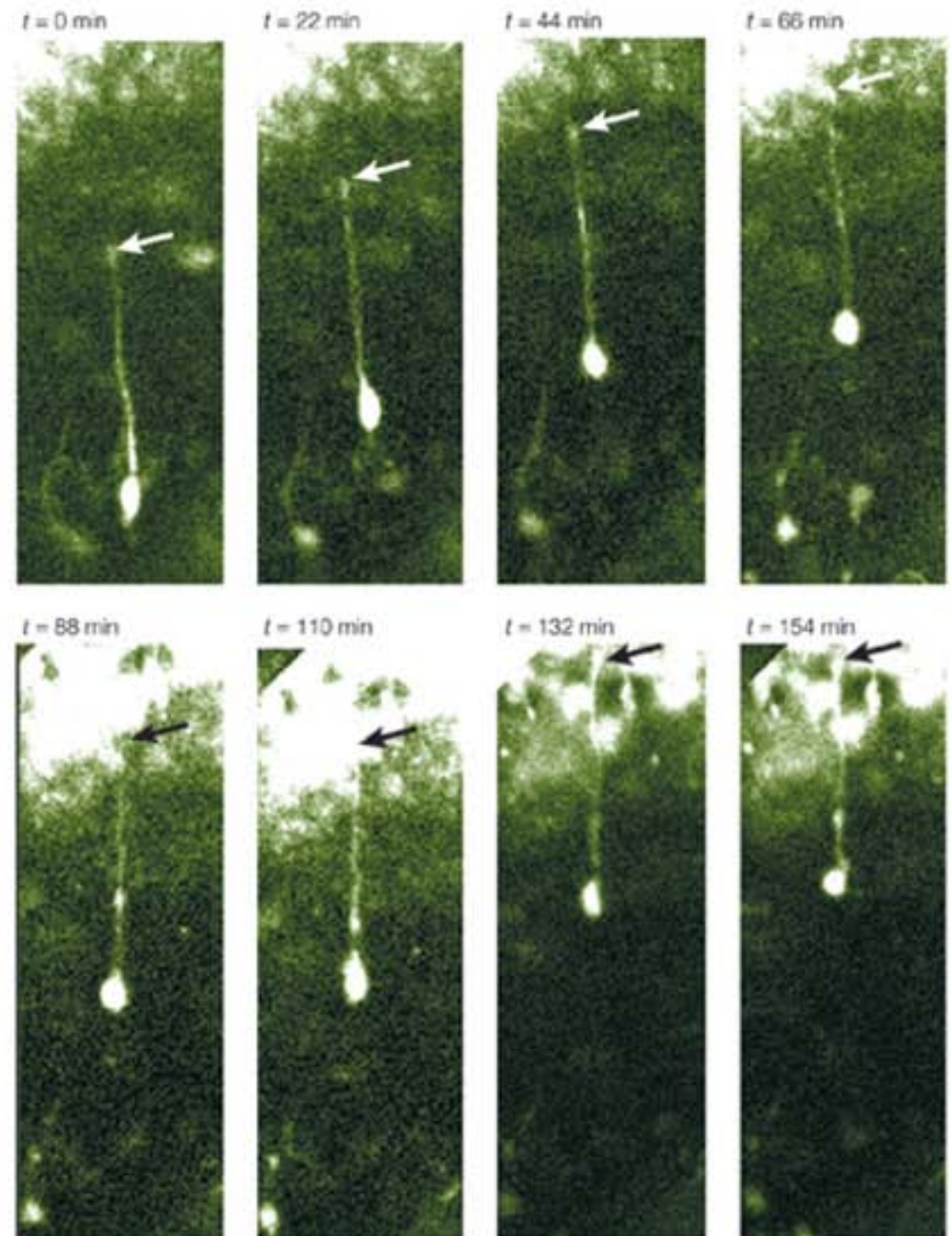
Glia-guided locomotion

Glial-Guidance

recording time: 160 min

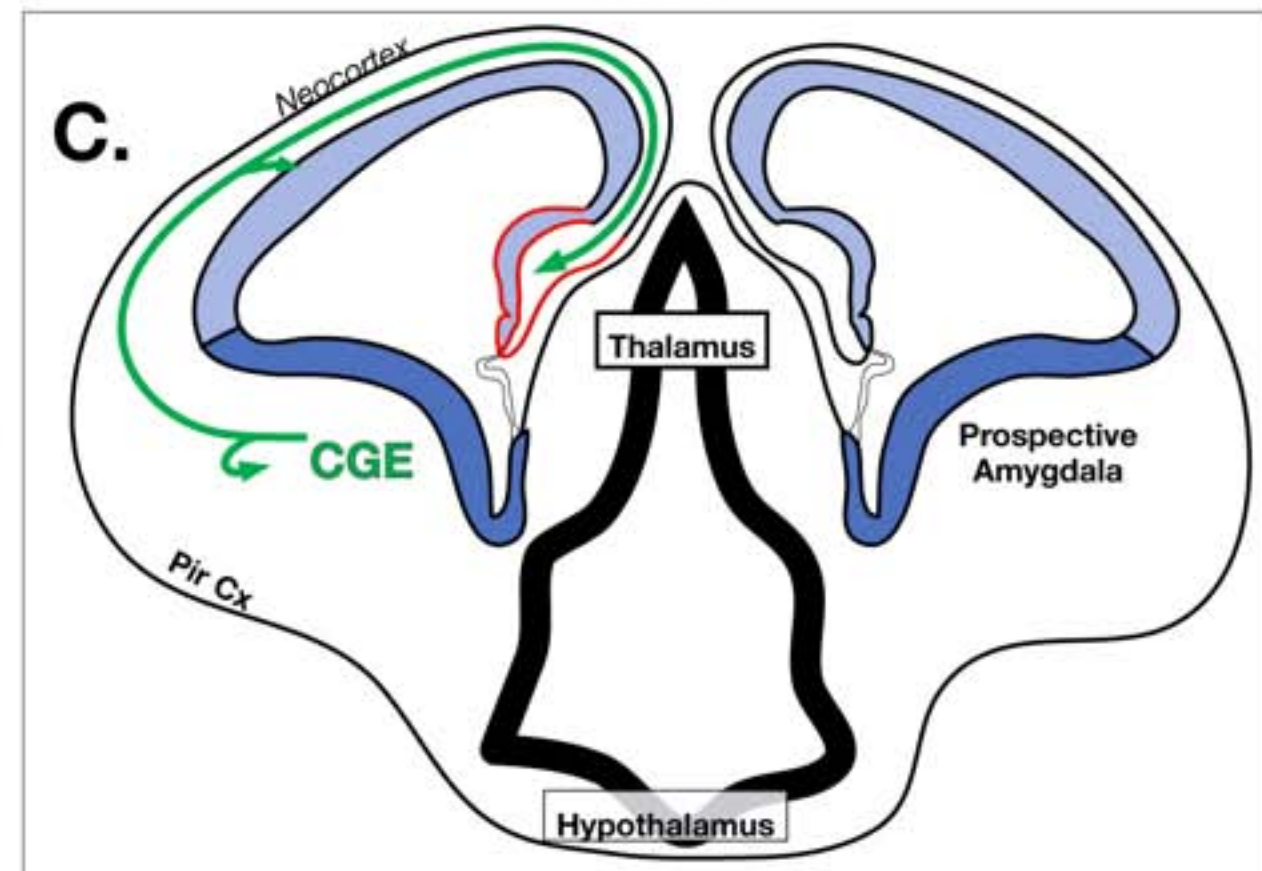
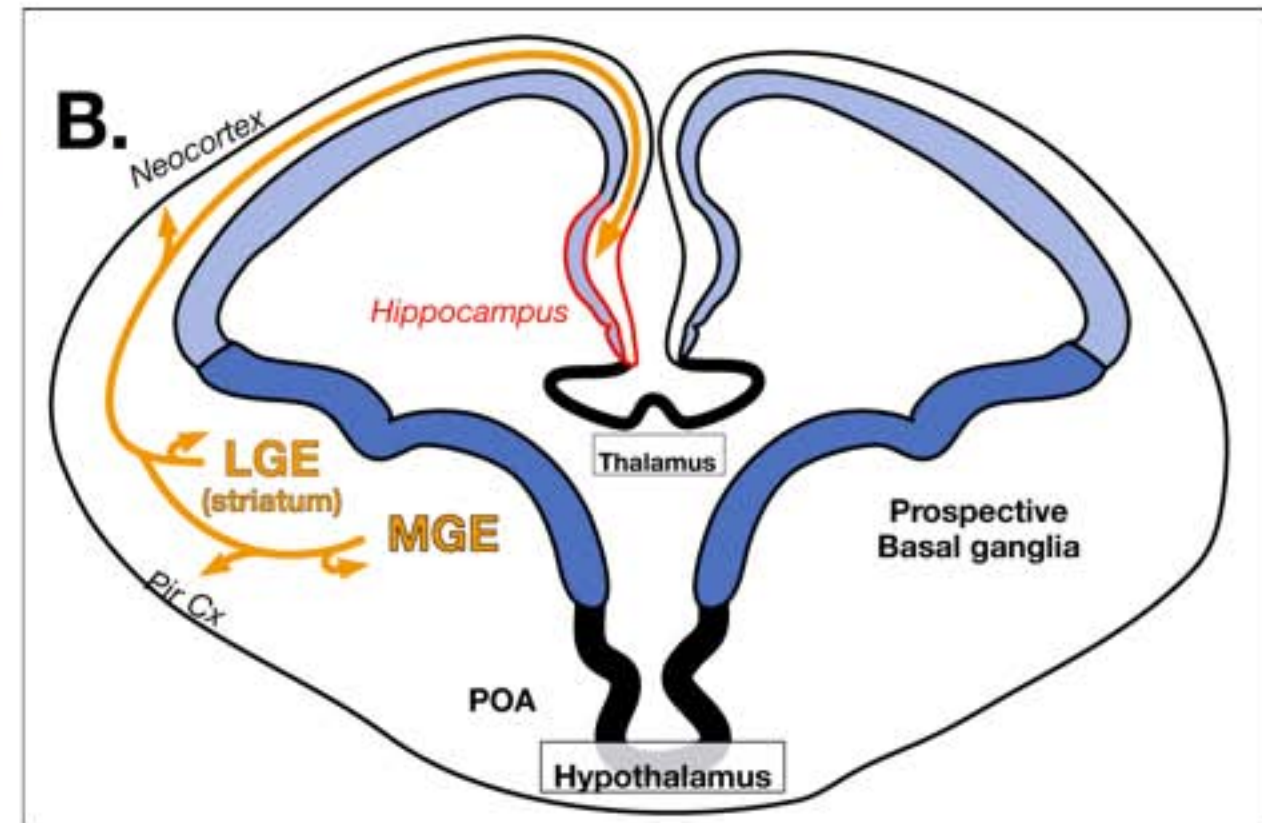
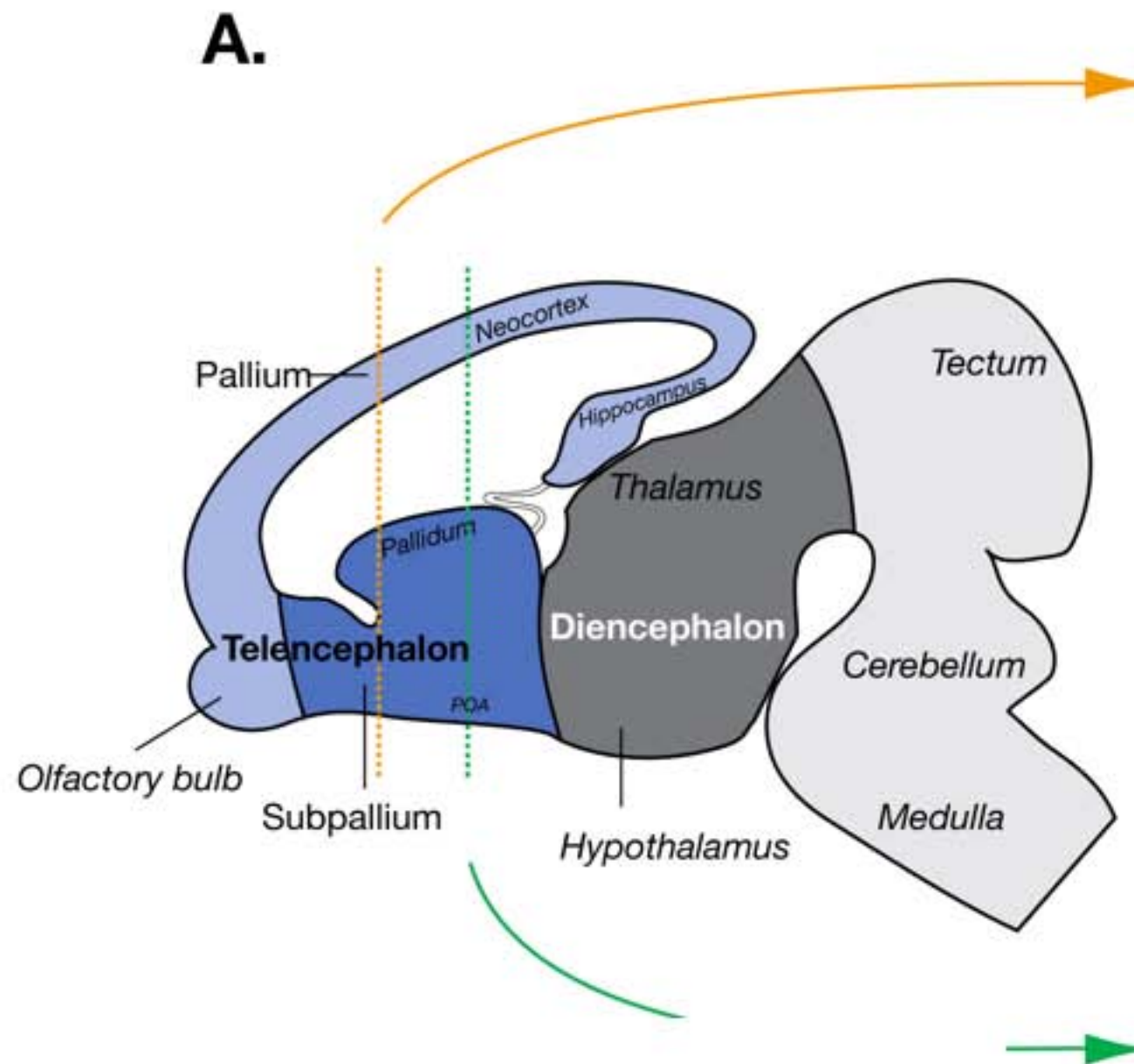
Nadarajah, Nature Neurosci. 4, 143–150 (2001).

Nadarajah & Parnavelas
Nat Rev Neur (2002)vol.3:423.



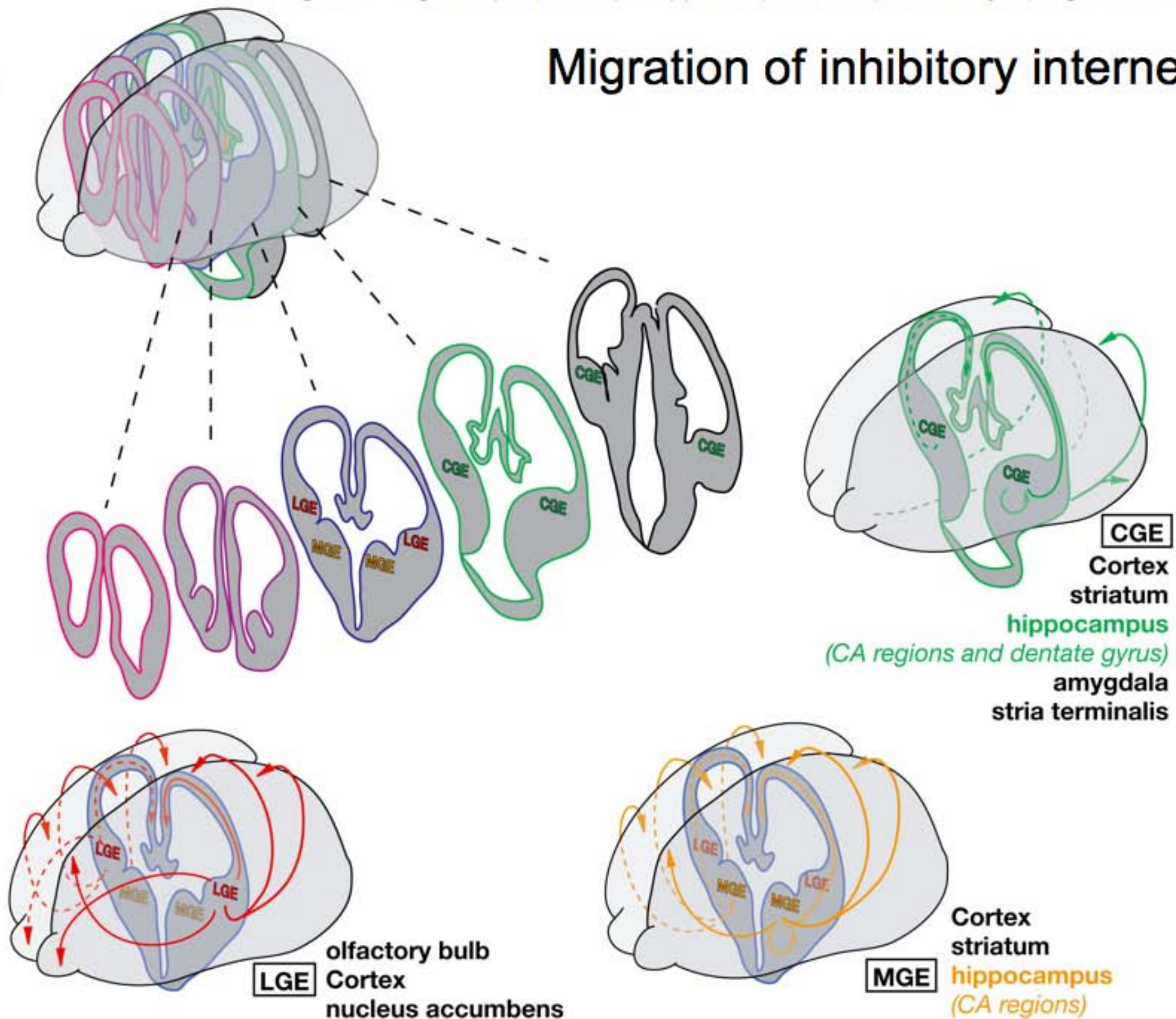
Modes of migration of inhibitory cells

Migration of inhibitory interneurons



D.

Migration of inhibitory interneurons



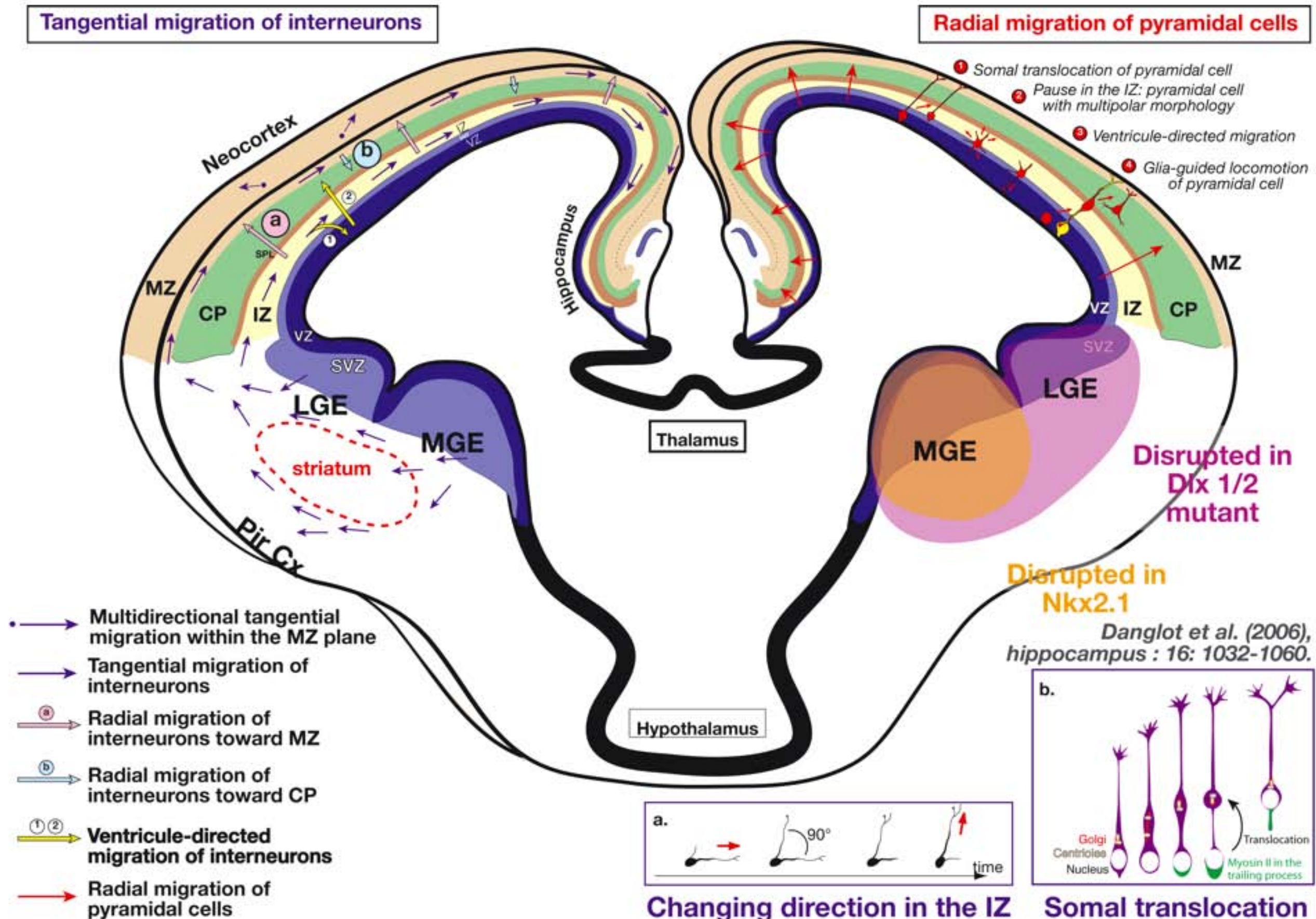
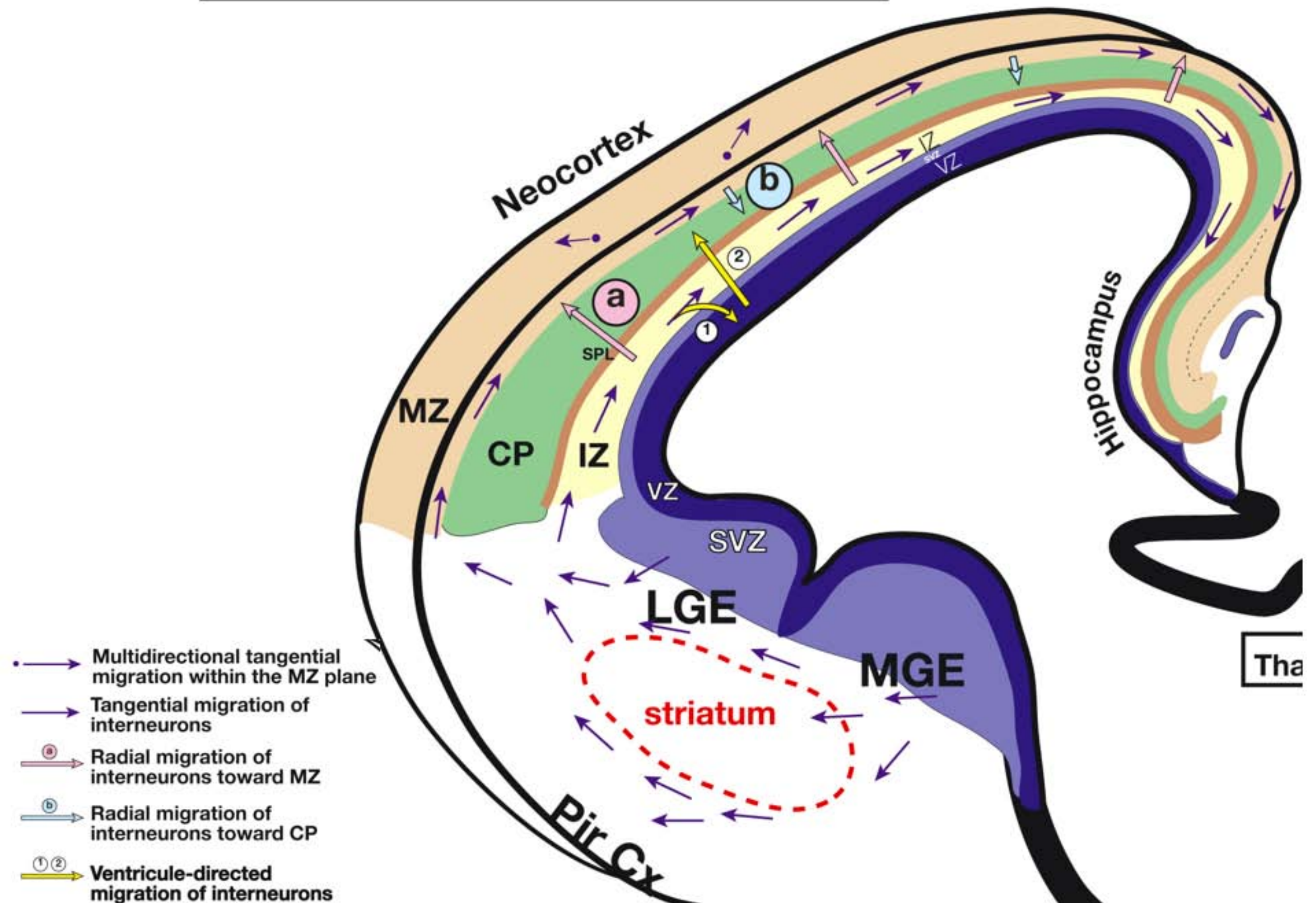


Figure 5 : Modes of migration of interneurons from the subpallial telencephalon toward the cortical and hippocampal anlagen.

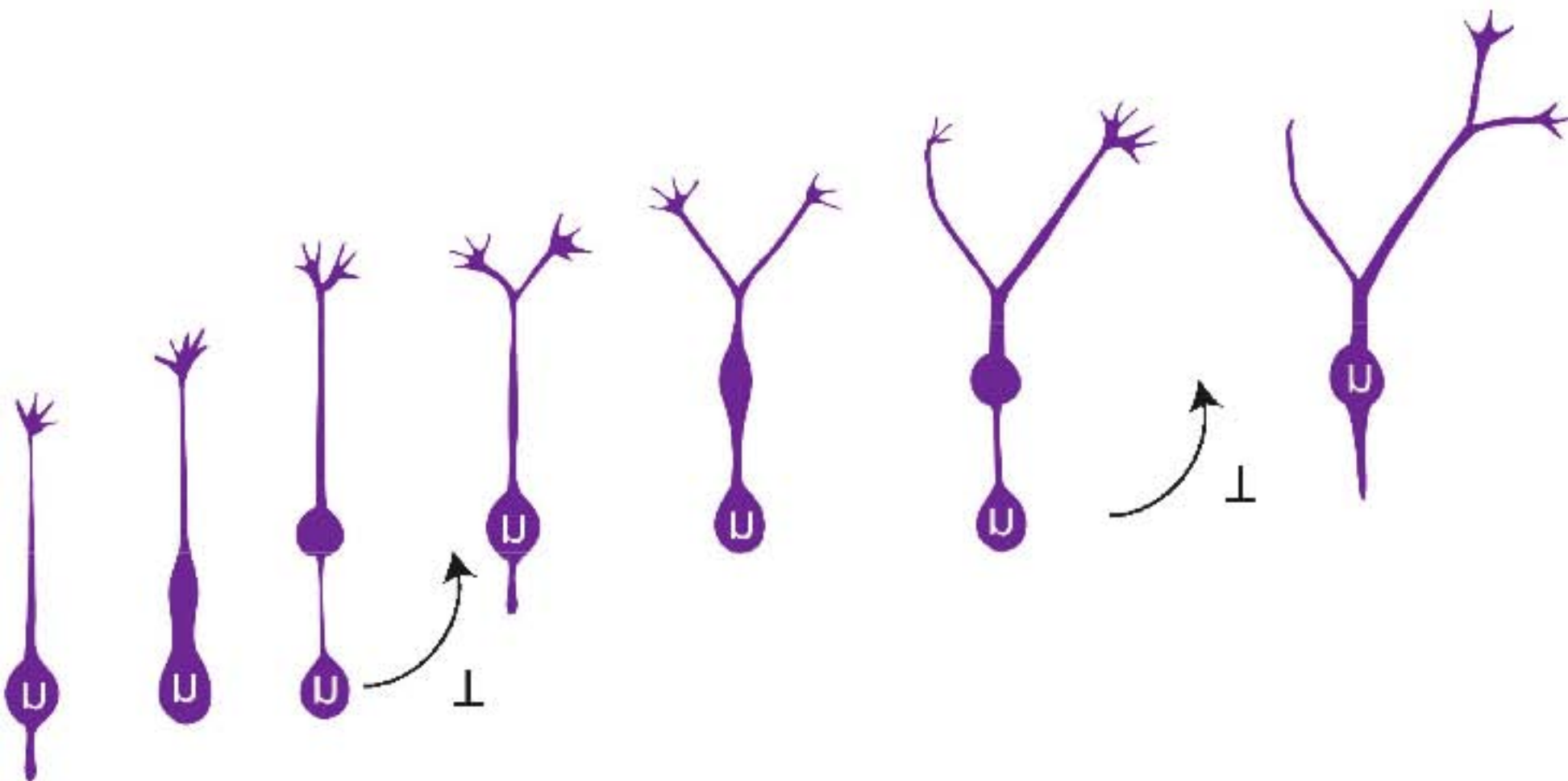
Tangential migration of interneurons



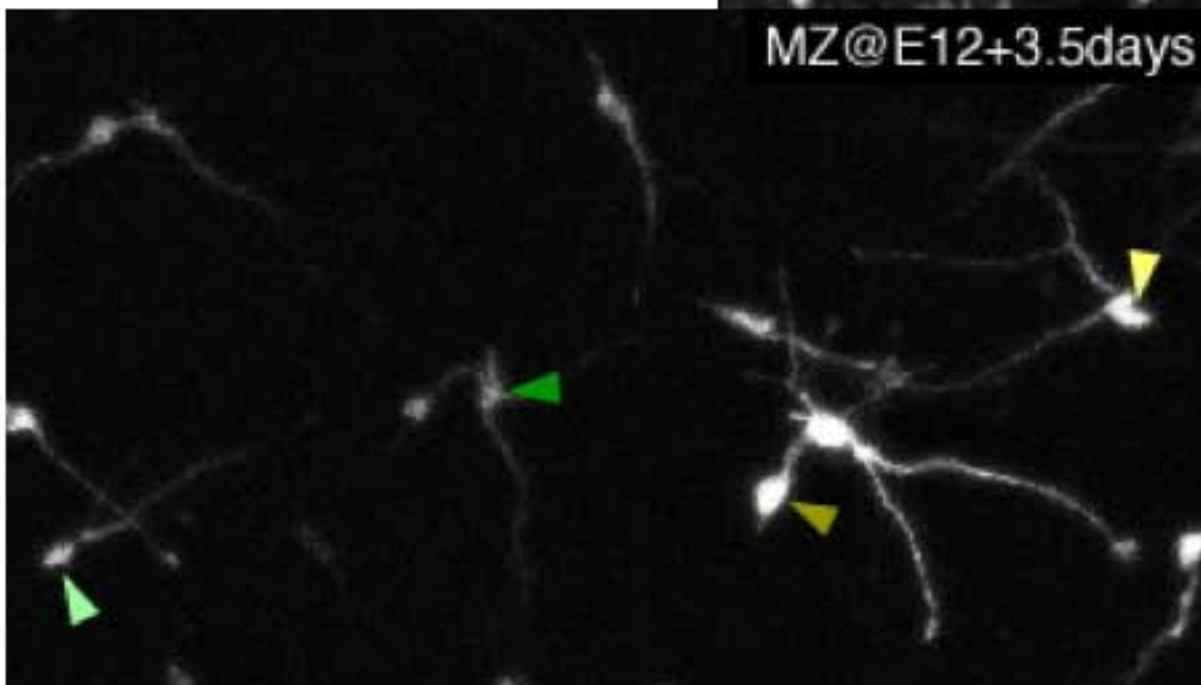
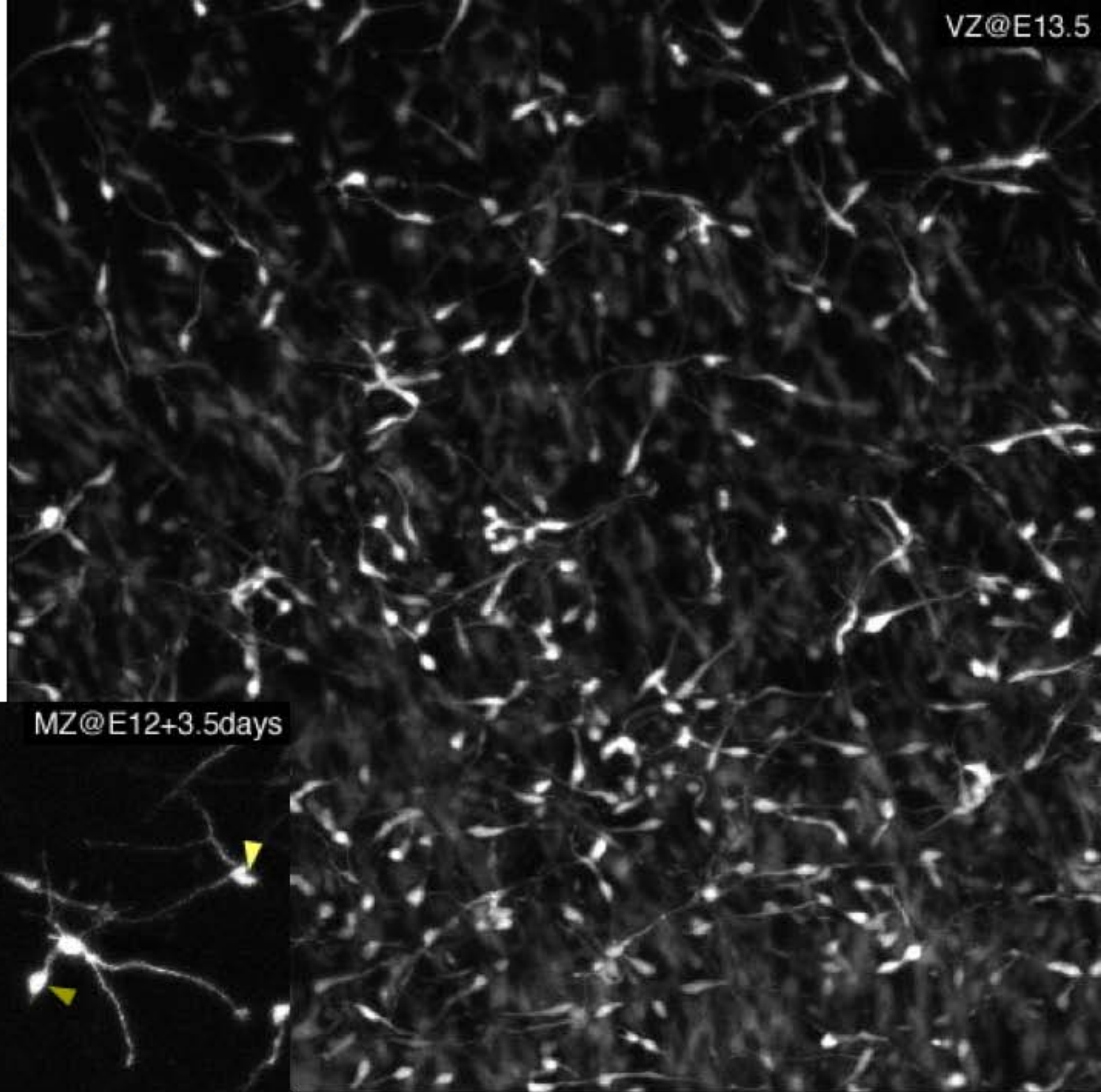
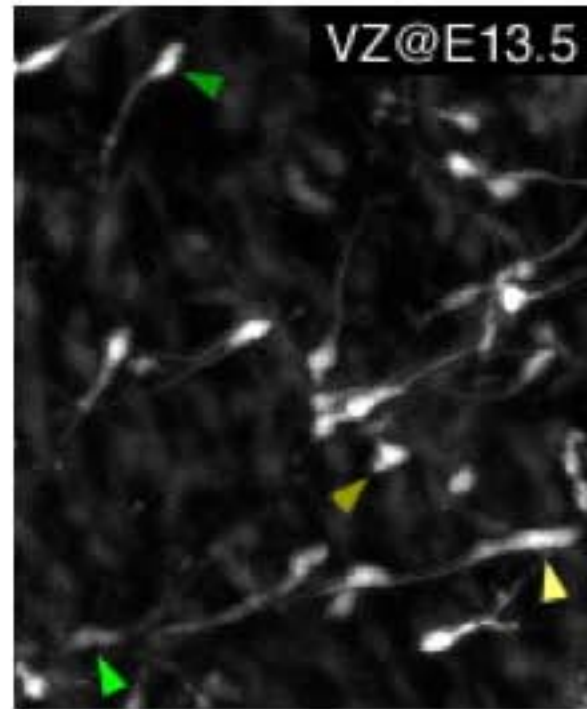
REVIEW ARTICLE

Cell and molecular mechanisms involved in the migration of cortical interneurons

Christine Métin,^{1,2} Jean-Pierre Baudoin,^{1,2} Sonja Rakić³ and John G. Parnavelas³

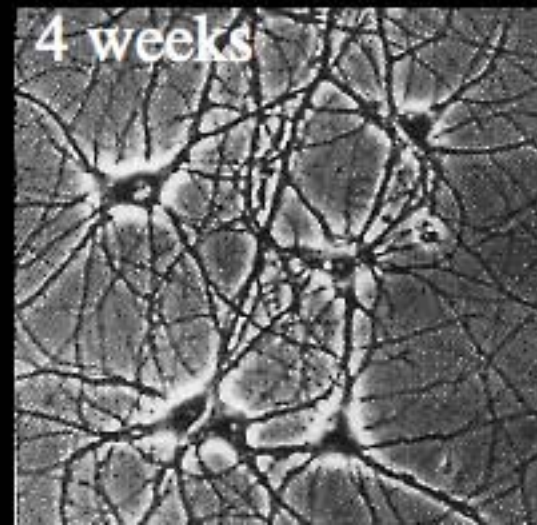
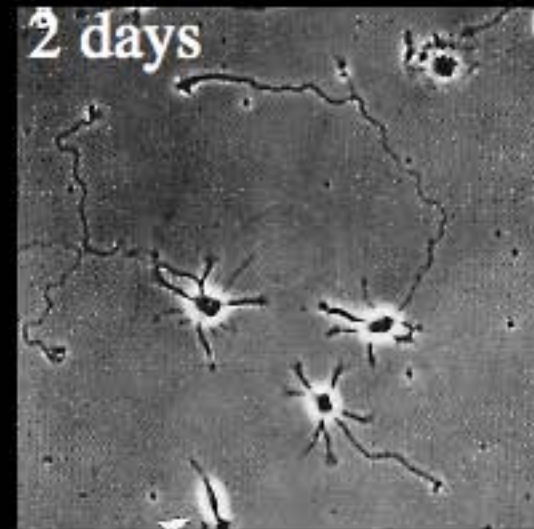
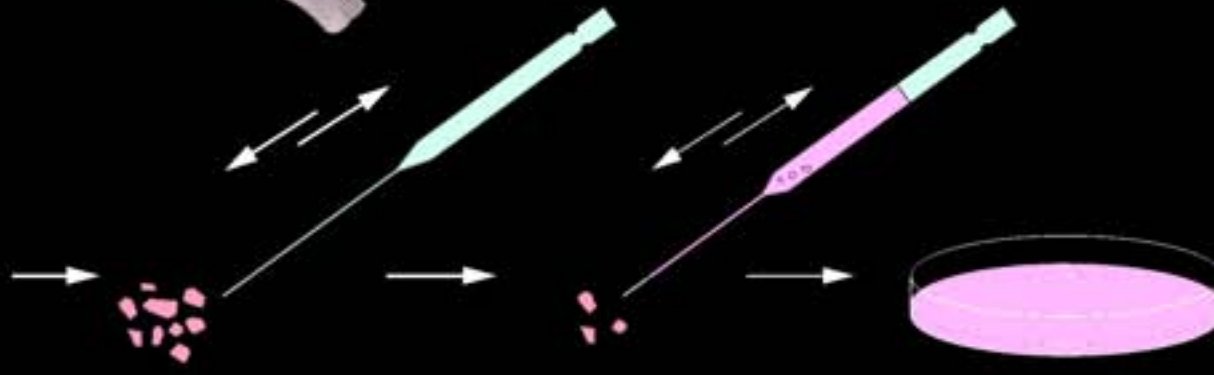
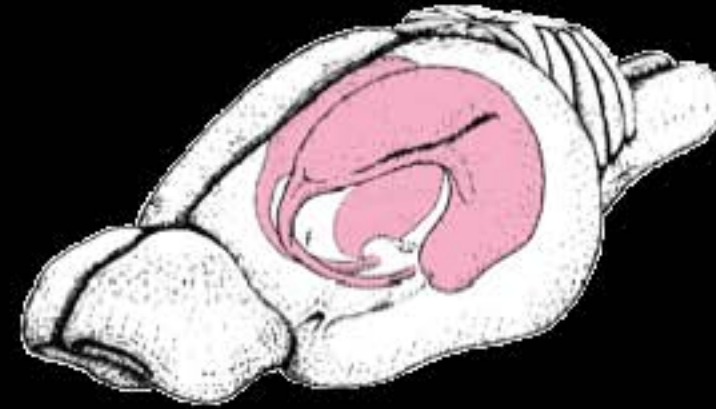
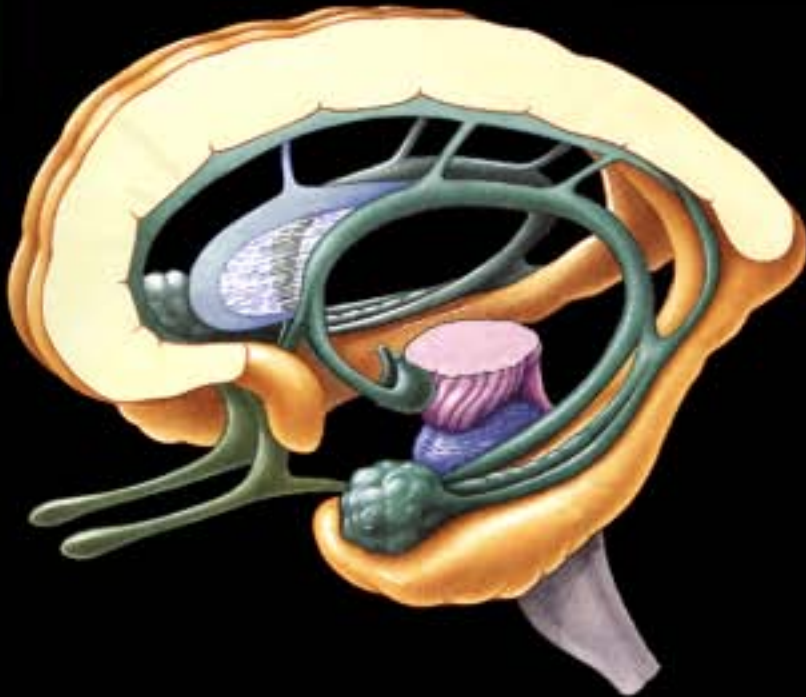


Multidirectional and
multizonal tangential
migration of GABAergic
interneurons in the
developing cerebral cortex
Development 133, 2167-2176 (2006)



Synaptogenesis

Hippocampal neurons in culture



Days
in vitro

0,25

0,5

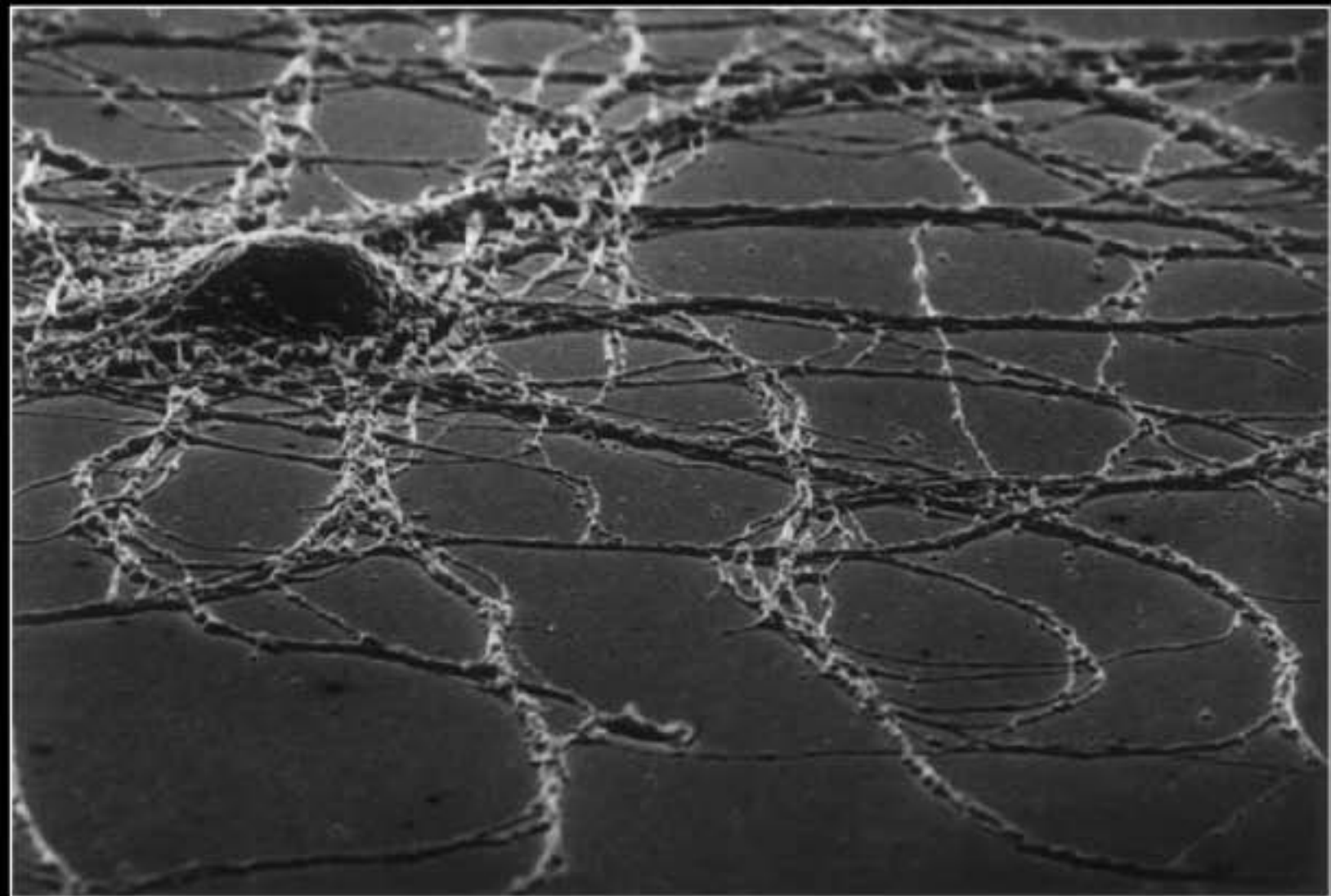
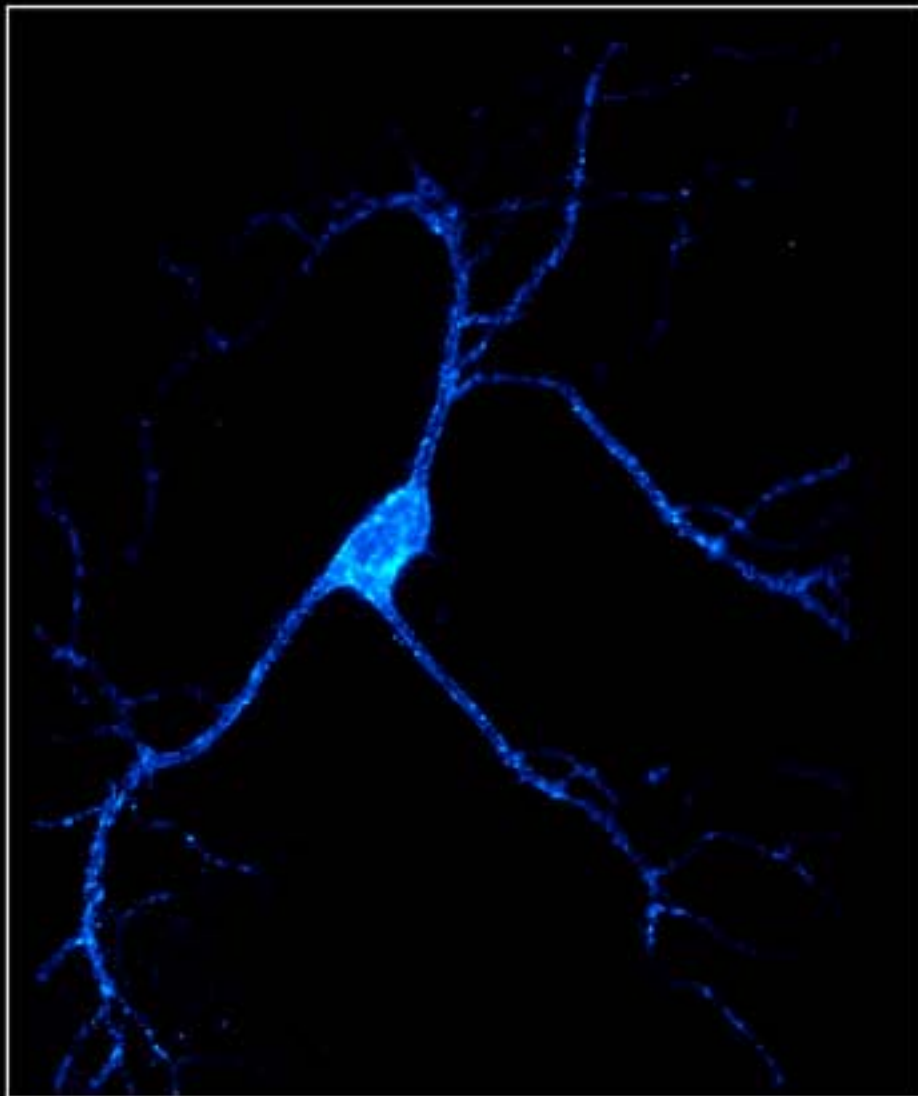
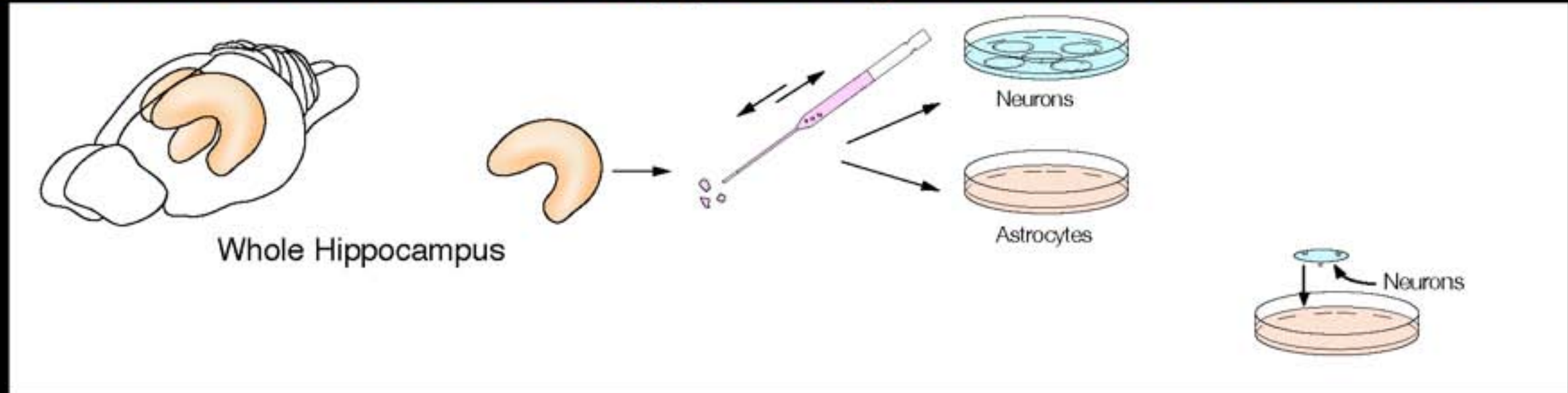
1,5

4

>7



The sandwich model of Hippocampal neurons in culture



Jours en culture :

0,25

0,5

1,5

4

> 7

Stades :

1
Lamelipodes

2
Neurites mineurs

3
Croissance axonale

4
Croissance dendritique

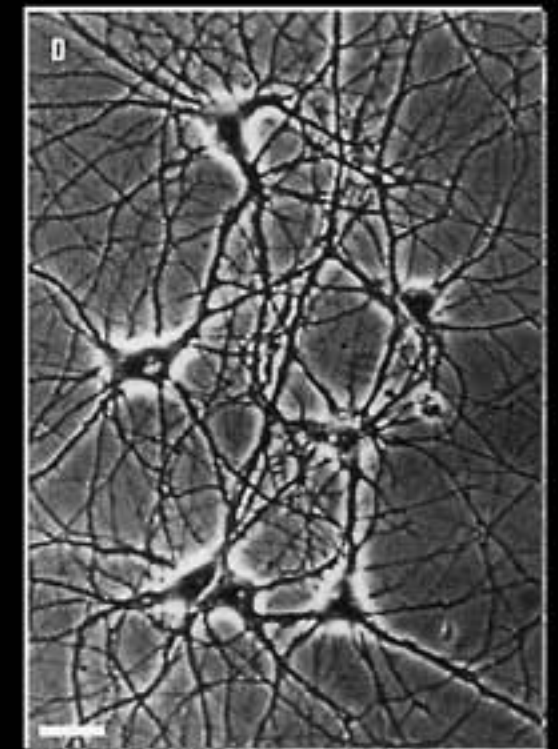
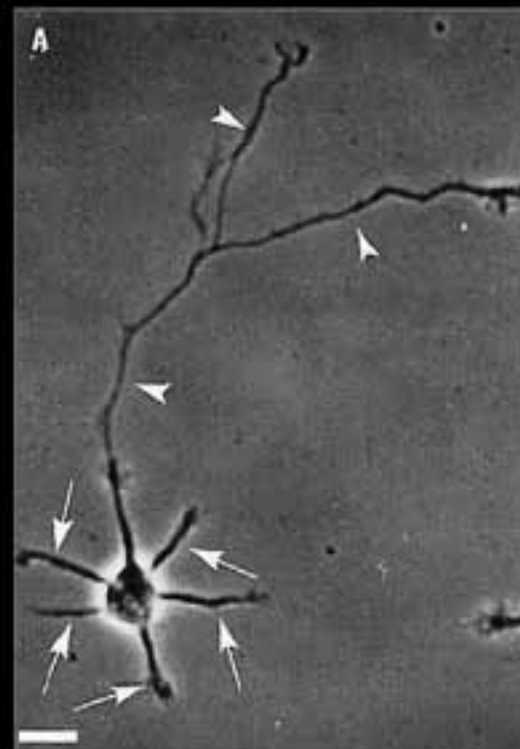
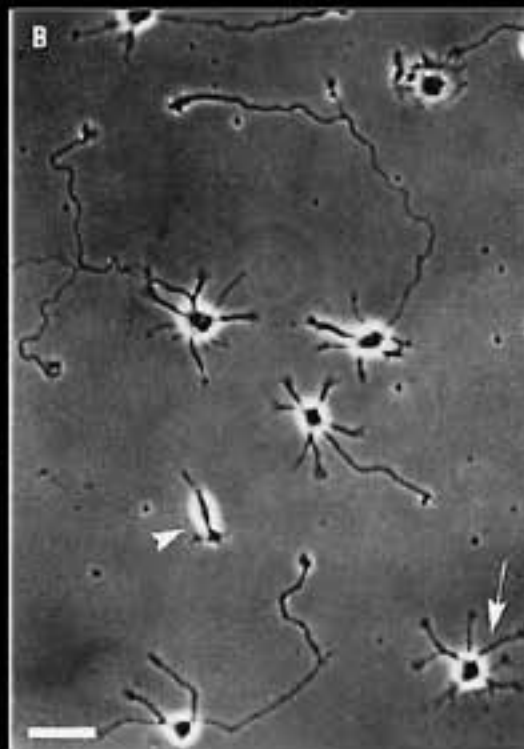
5
Maturation

DIV 18-21

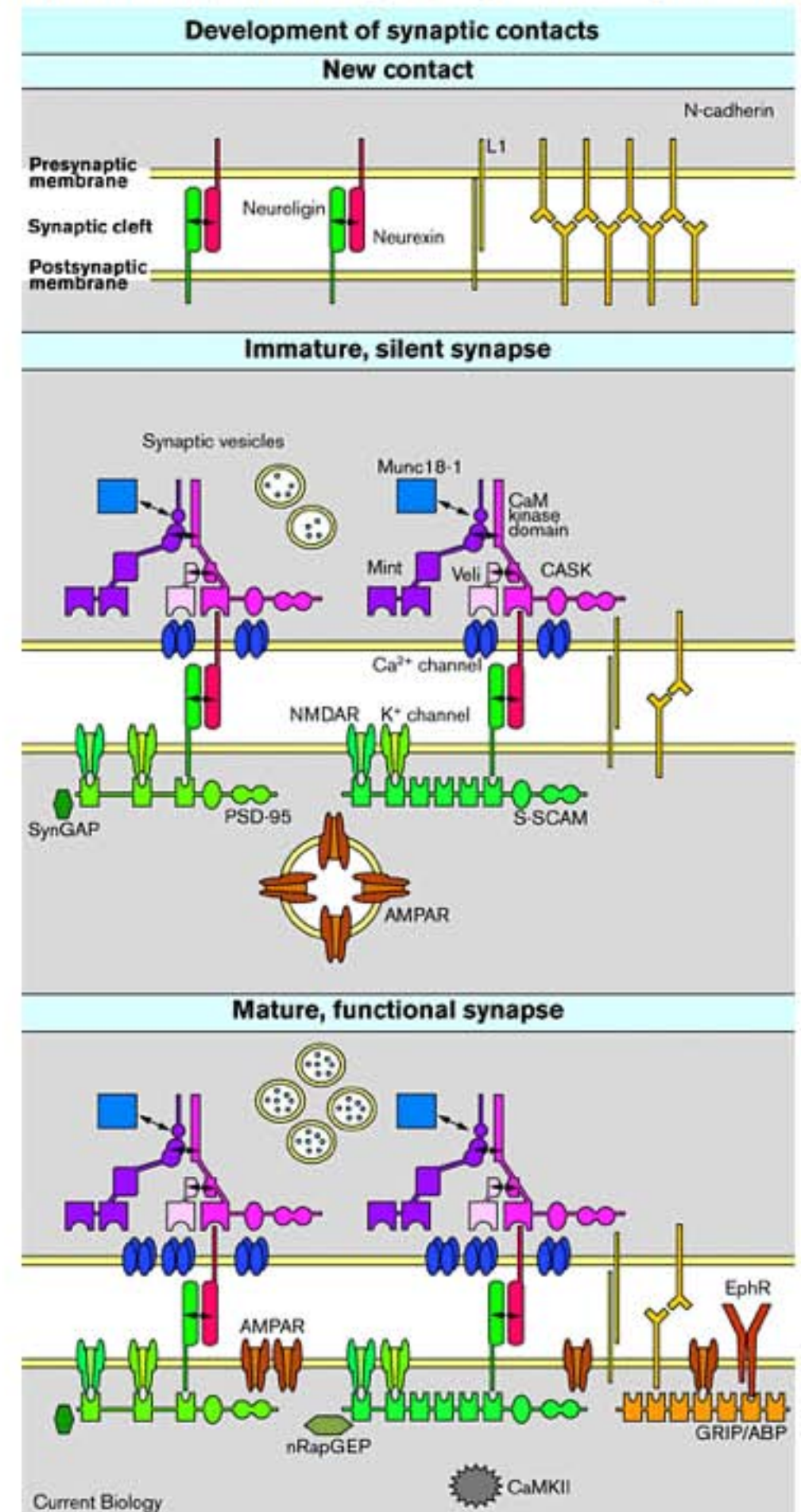
Axonal outgrowth
and polarisation

Dendrites outgrowth
Synaptogenesis with appearance of
axonal pre-synaptic boutons (swelling)
connecting dendrites/bodies

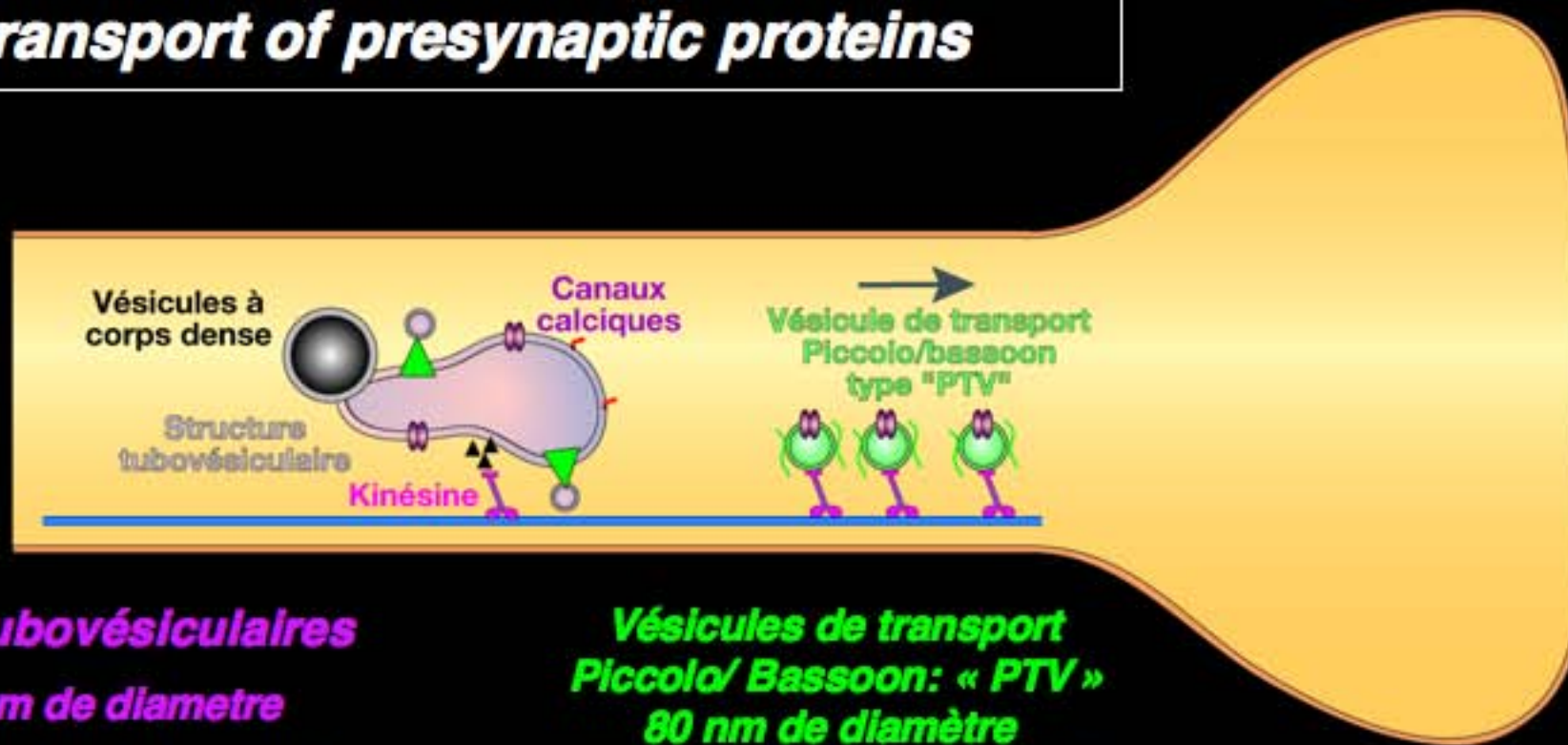
Onset of dendritic spines
development



Formation of the synapse



Axonal transport of presynaptic proteins



Structures tubovésiculaires

500-1500 nm de diamètre

Ahmari et coll., Nat Neur, 2000.

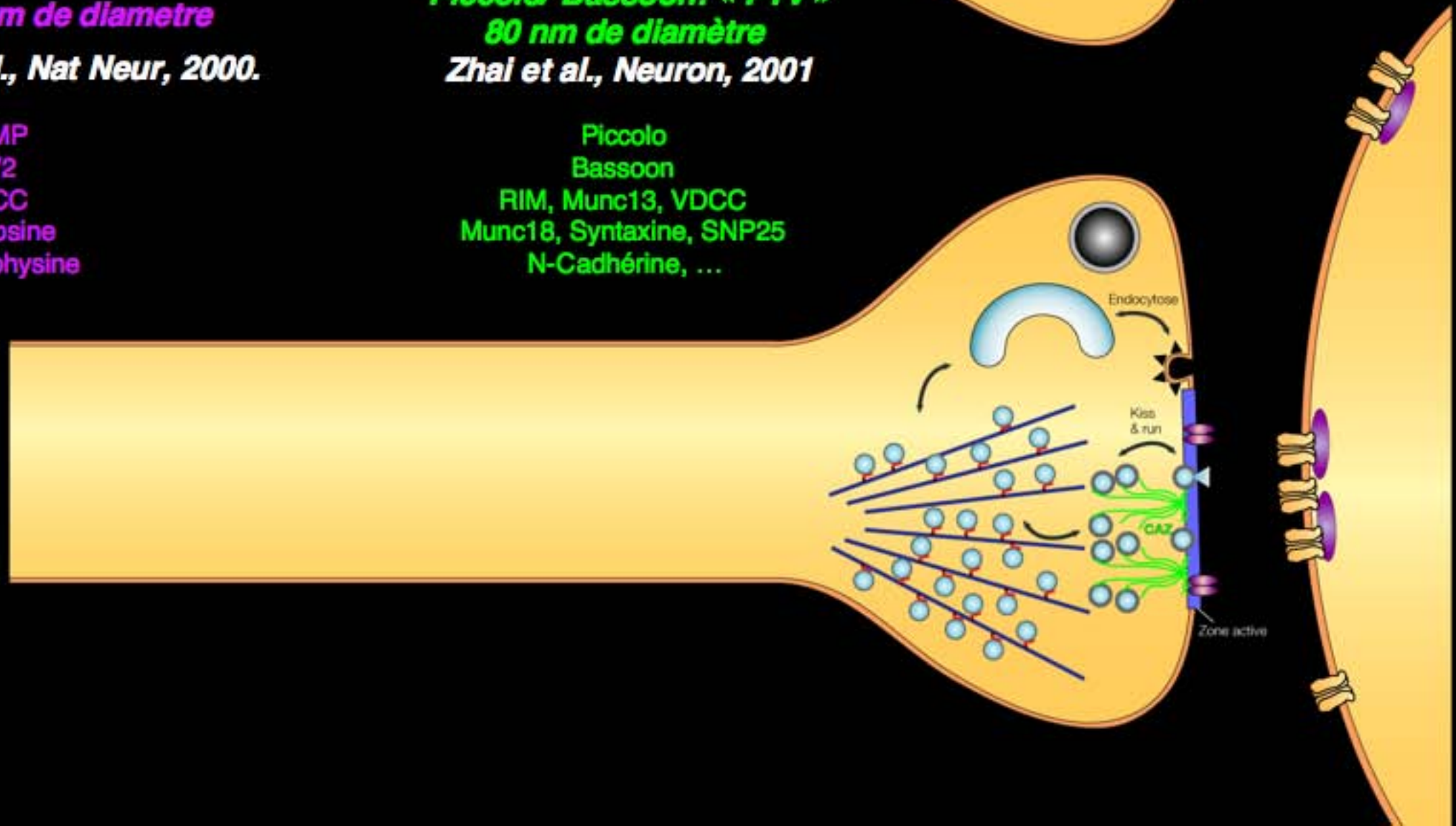
VAMP
SV2
VDCC
Synapsine
amphiphysine

Vésicules de transport Piccolo/ Bassoon: « PTV »

80 nm de diamètre

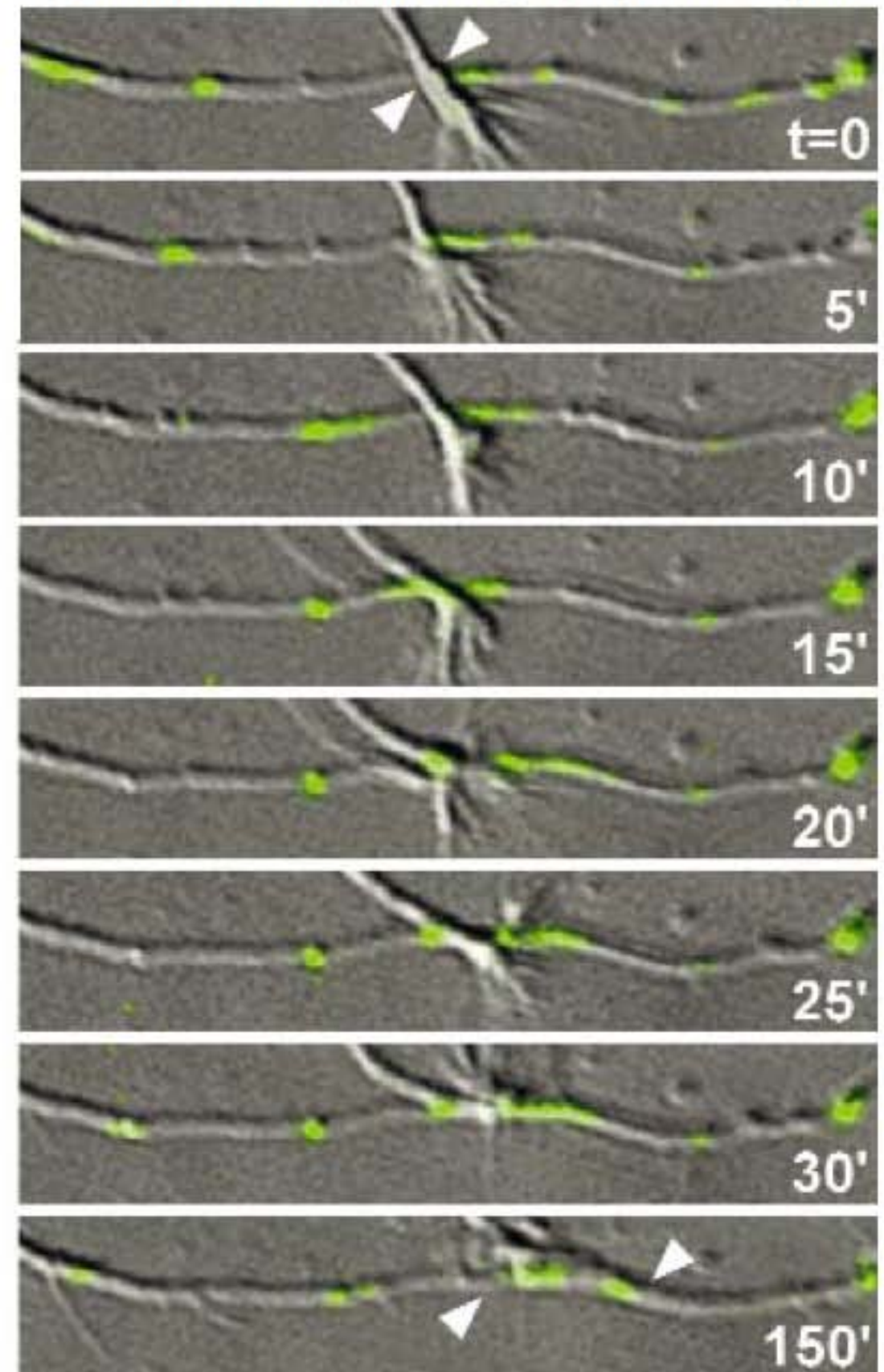
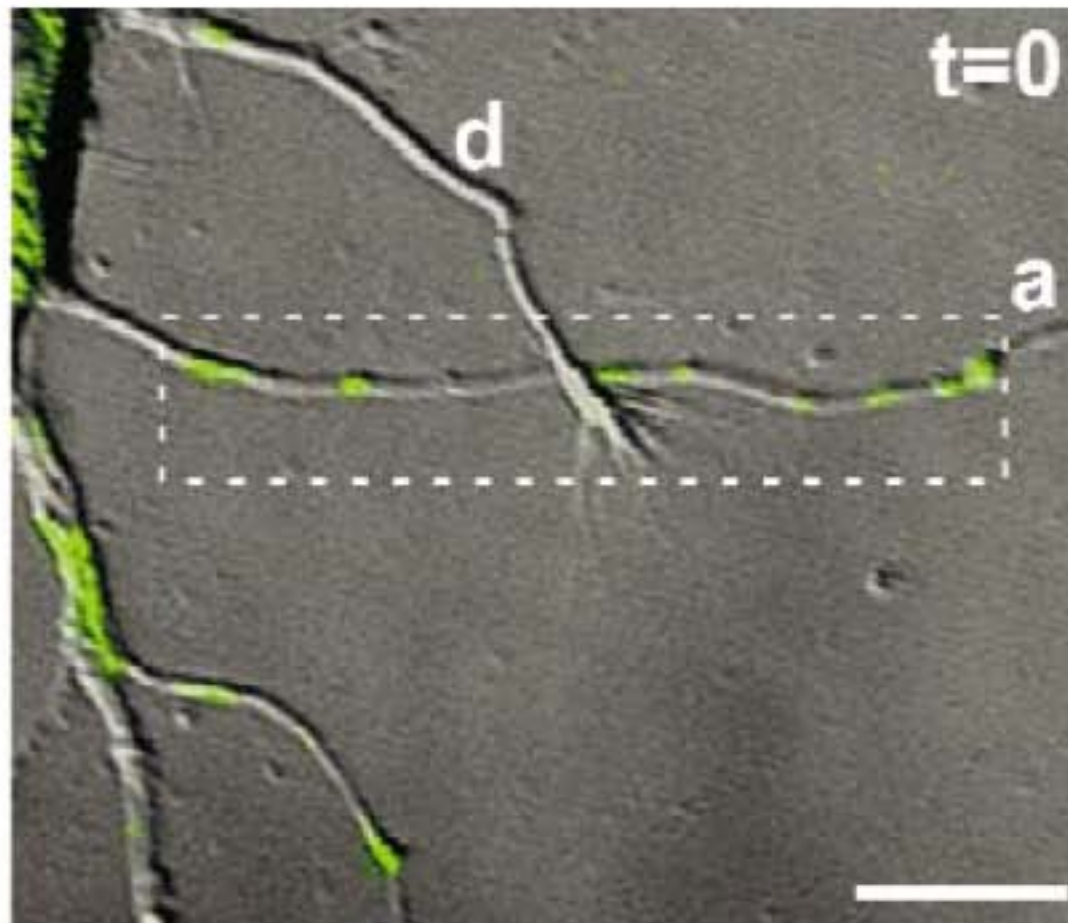
Zhai et al., Neuron, 2001

Piccolo
Bassoon
RIM, Munc13, VDCC
Munc18, Syntaxine, SNP25
N-Cadhérine, ...

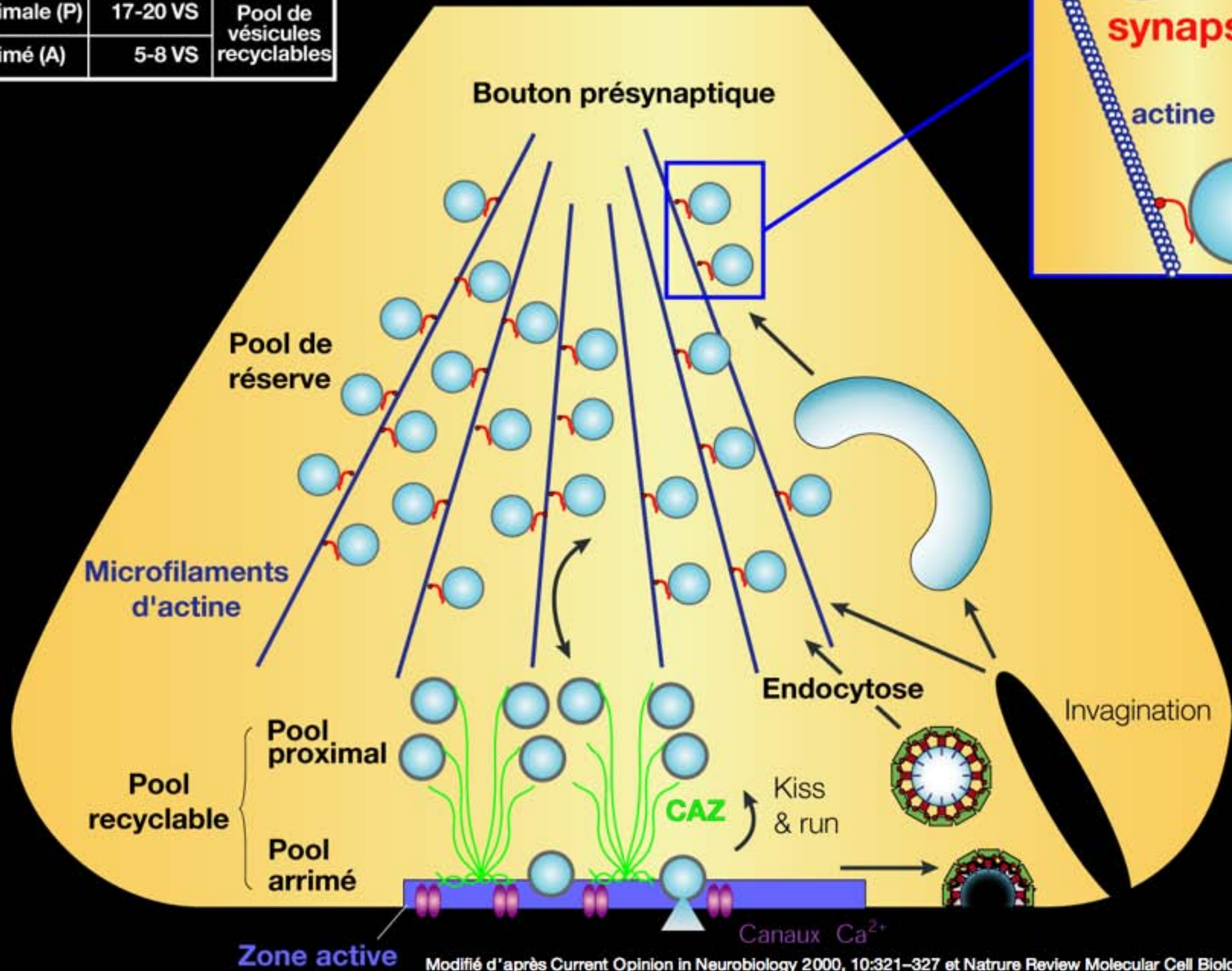


Assembly of presynaptic active zones from cytoplasmic transport packets

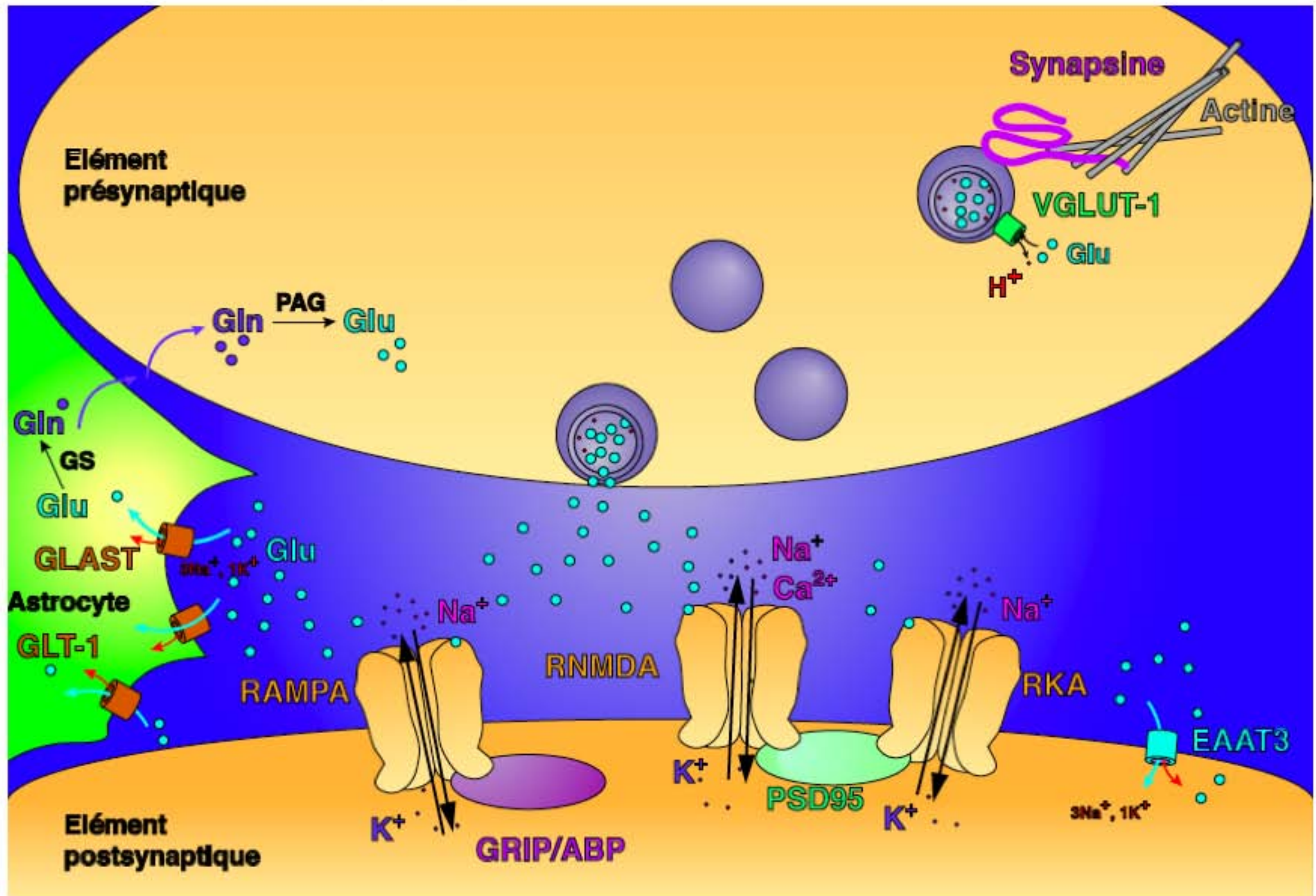
Susanne E. Ahmari, Jo Ann Buchanan and Stephen J Smith



Type de pool	Nombre de vésicules	
de réserve (R)	180 VS	
proximale (P)	17-20 VS	Pool de vésicules recyclables
arrimé (A)	5-8 VS	



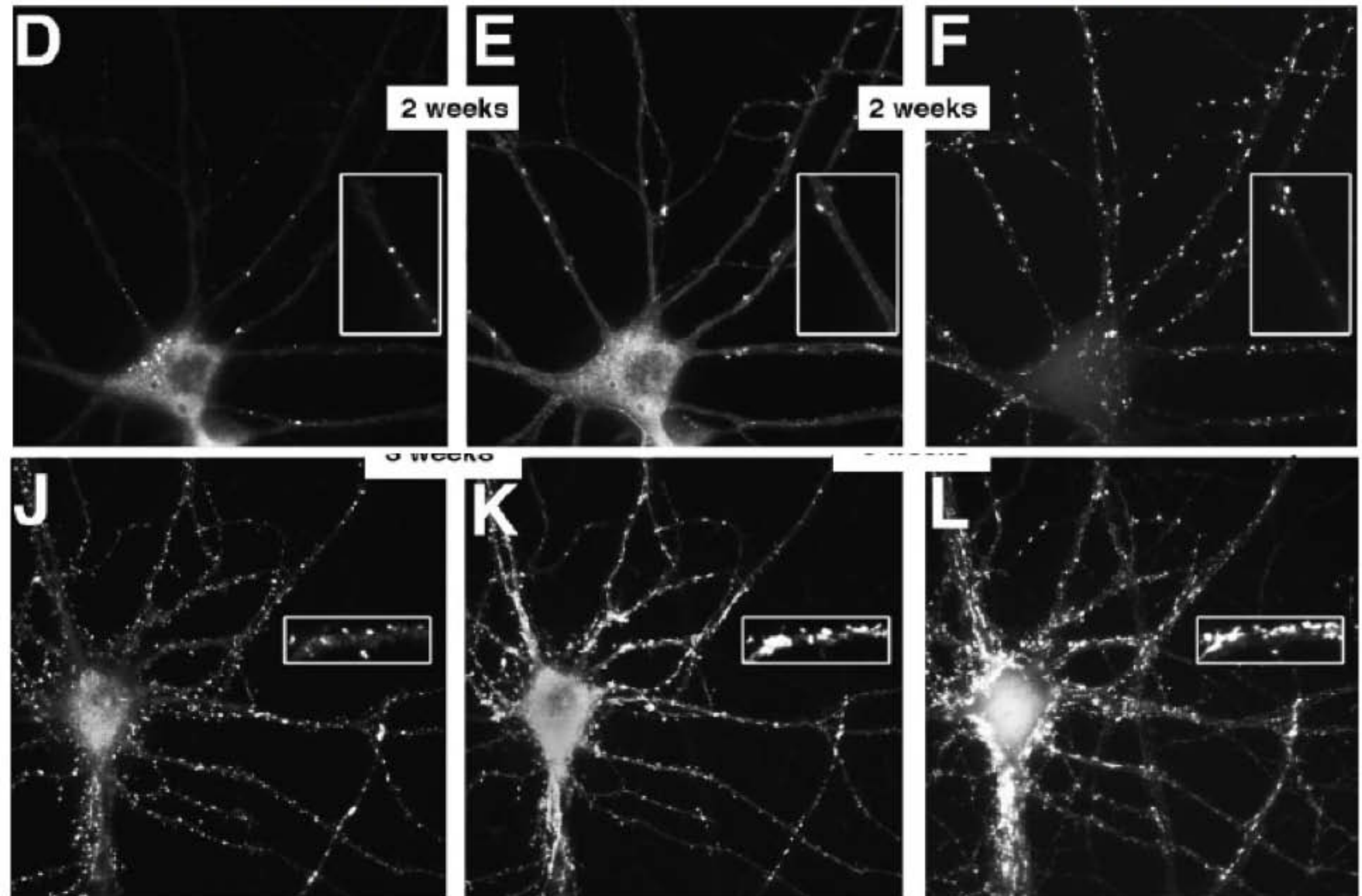
Glutamatergic synapse



NMDAR (NR1)

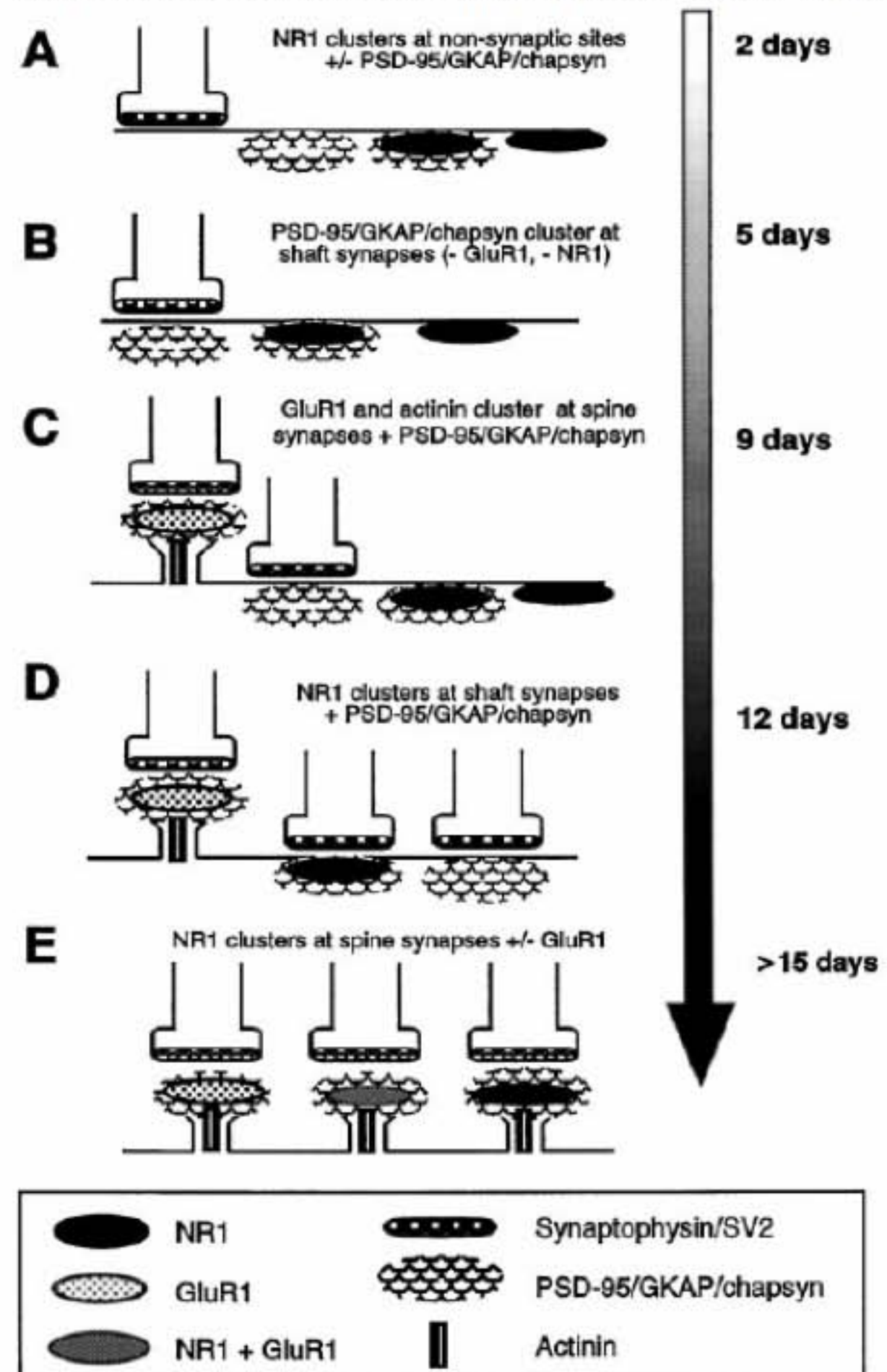
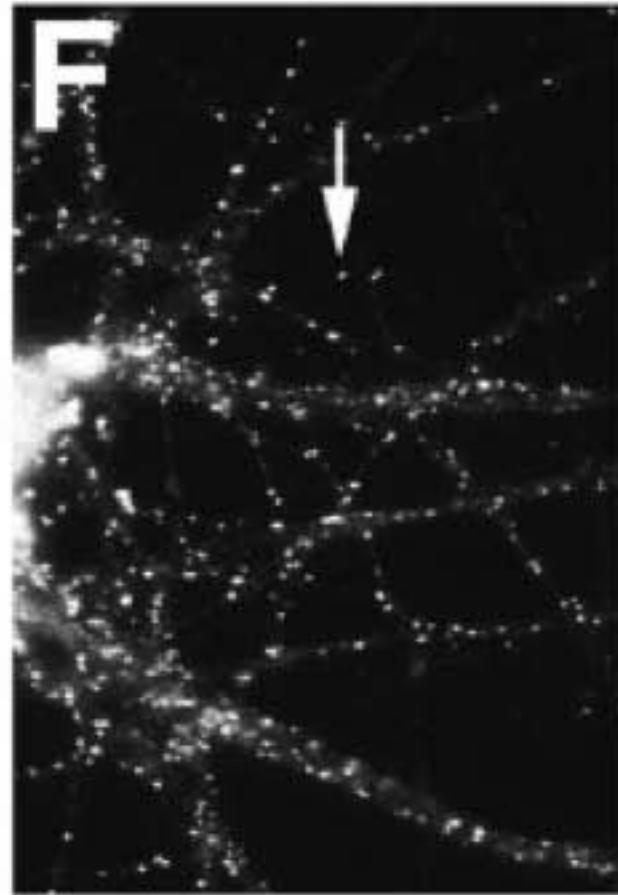
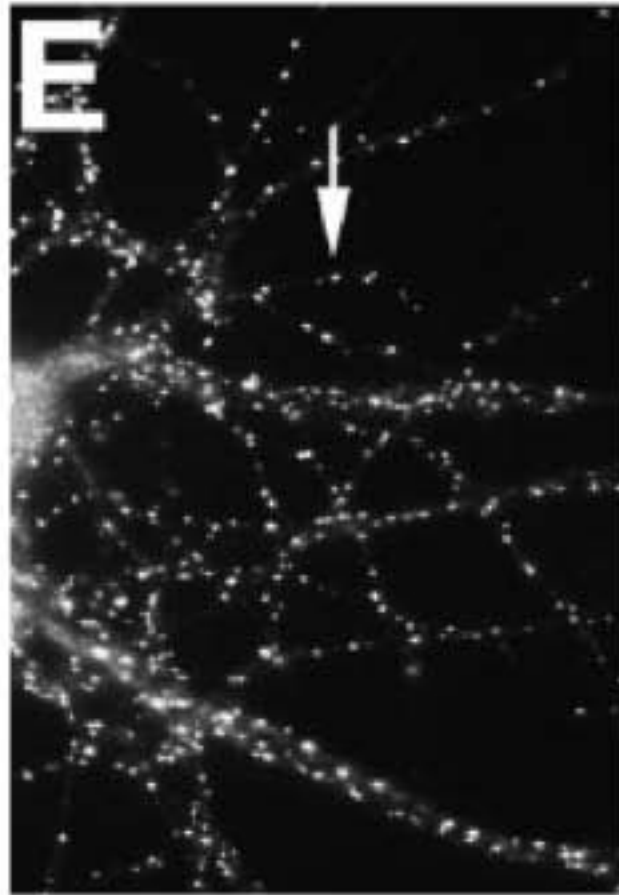
AMPA (GluR1)

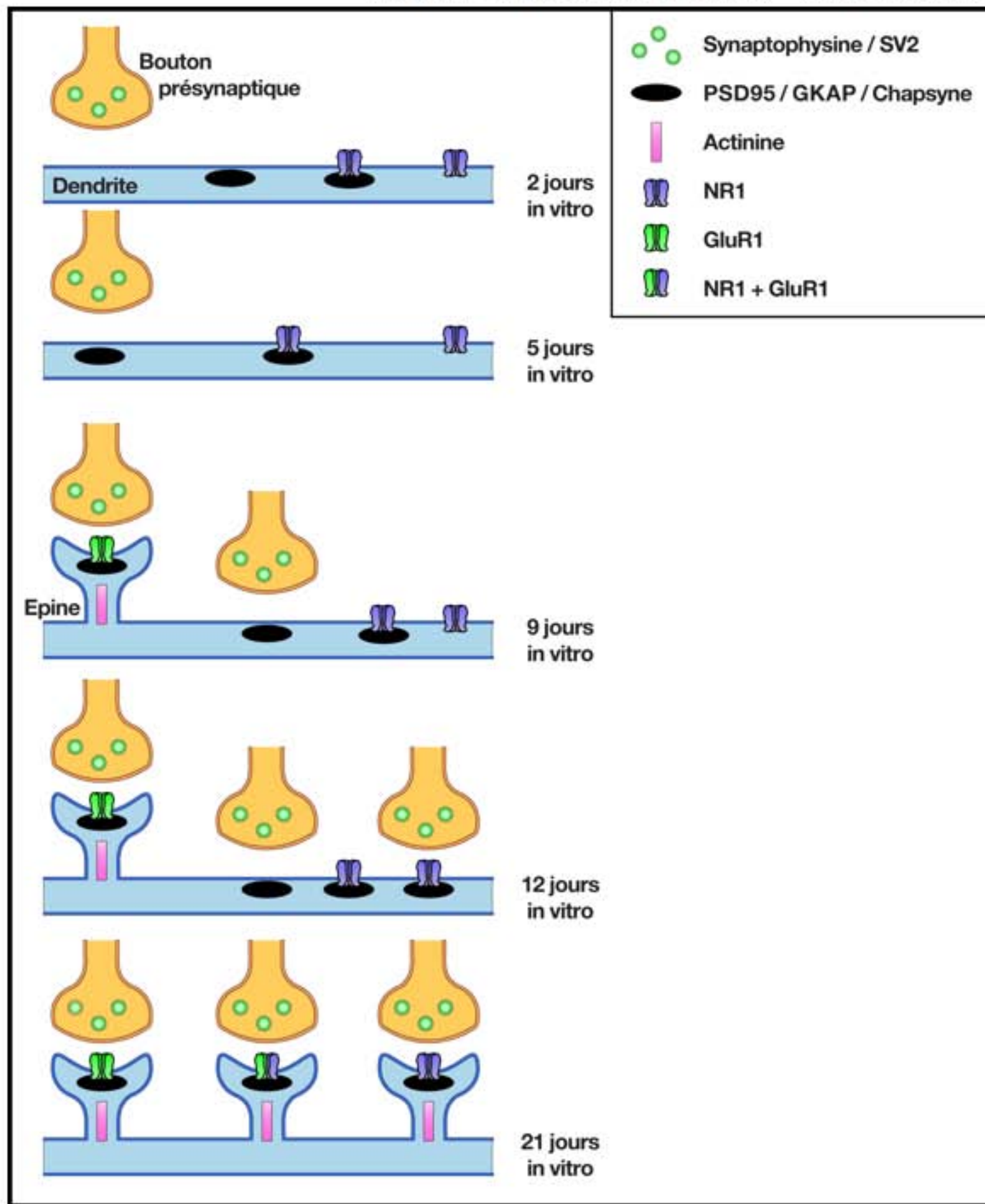
Synaptophysin

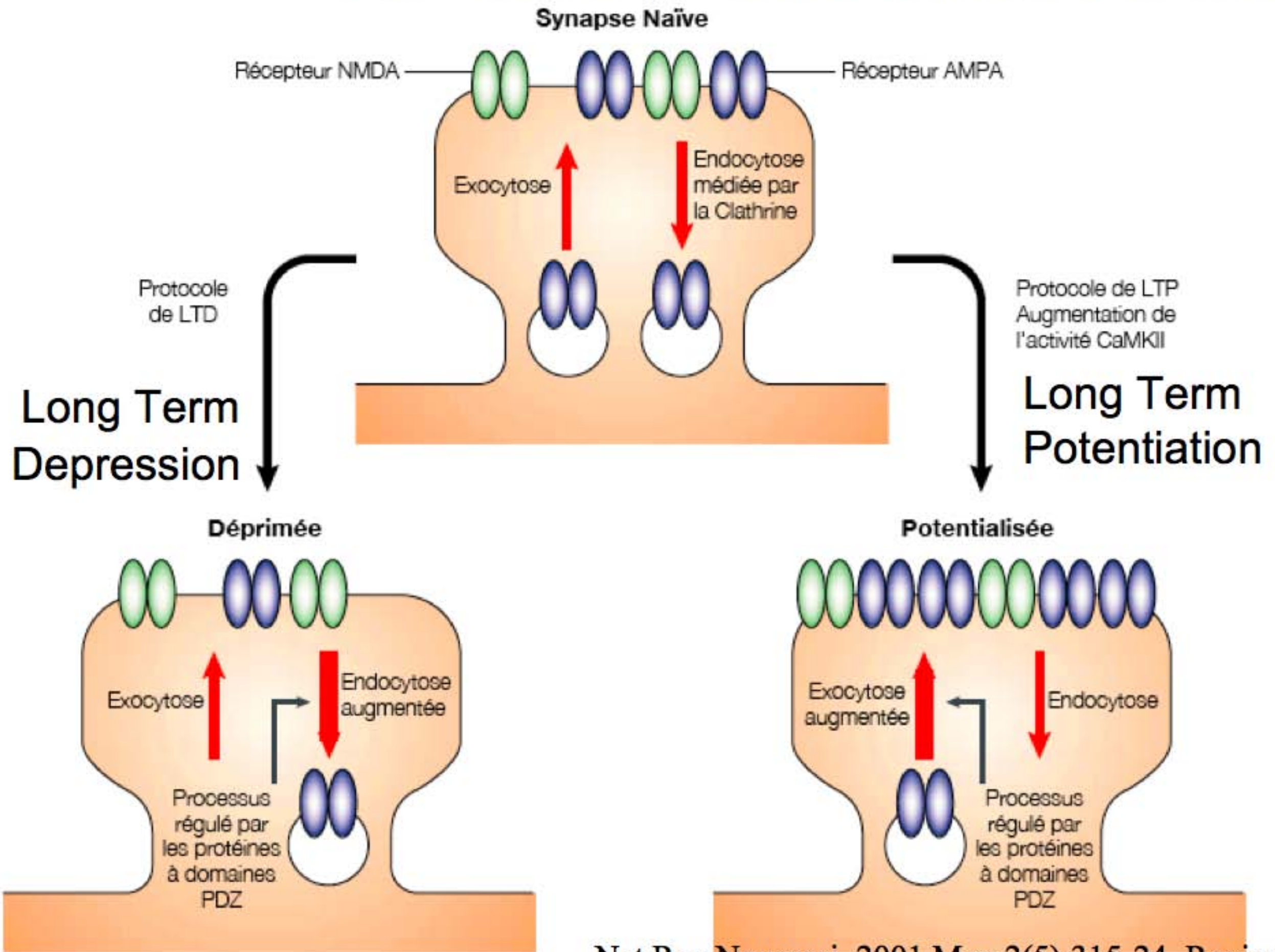


NMDAR (NR1)

PSD 95







NMDAR

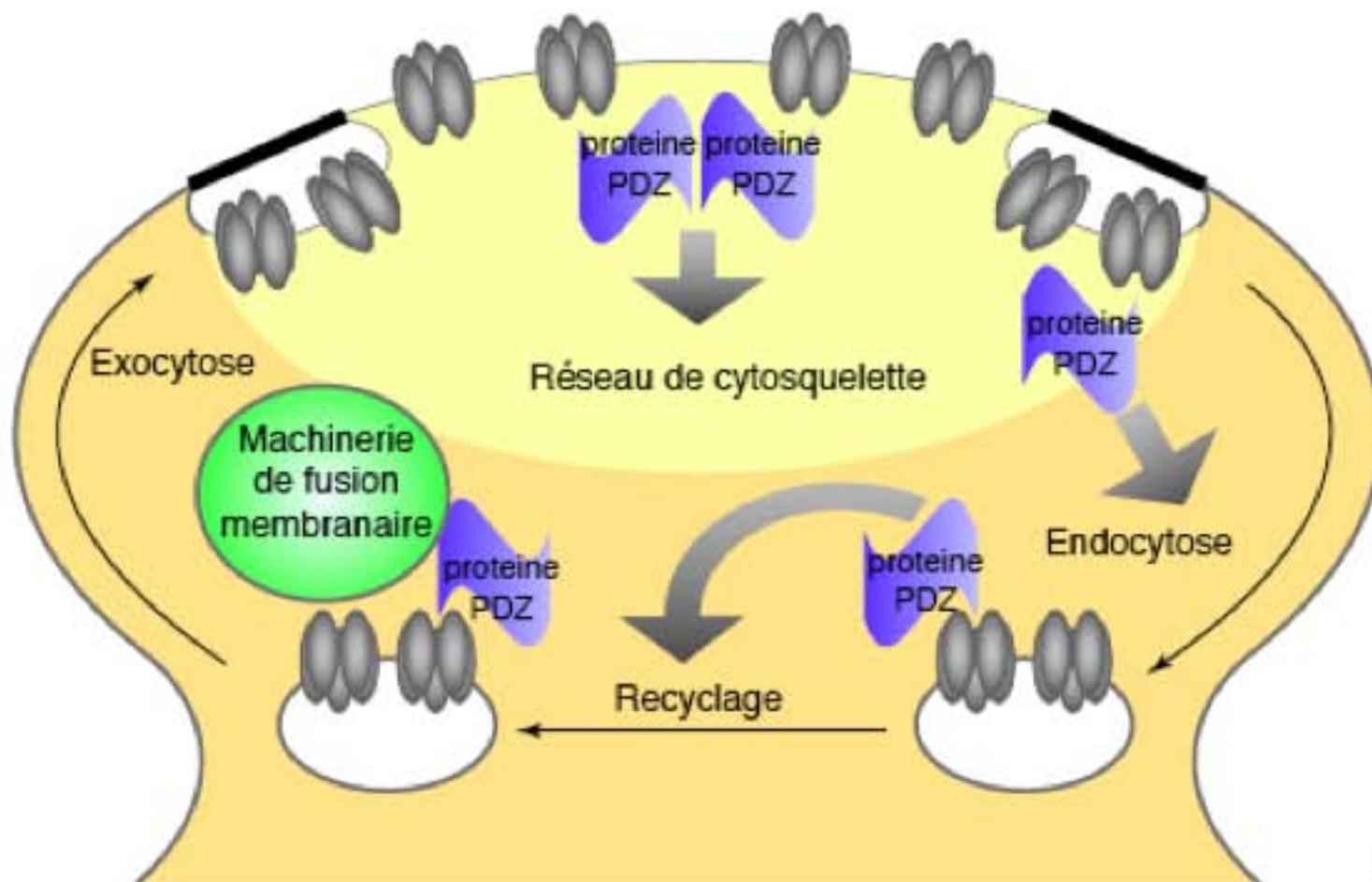
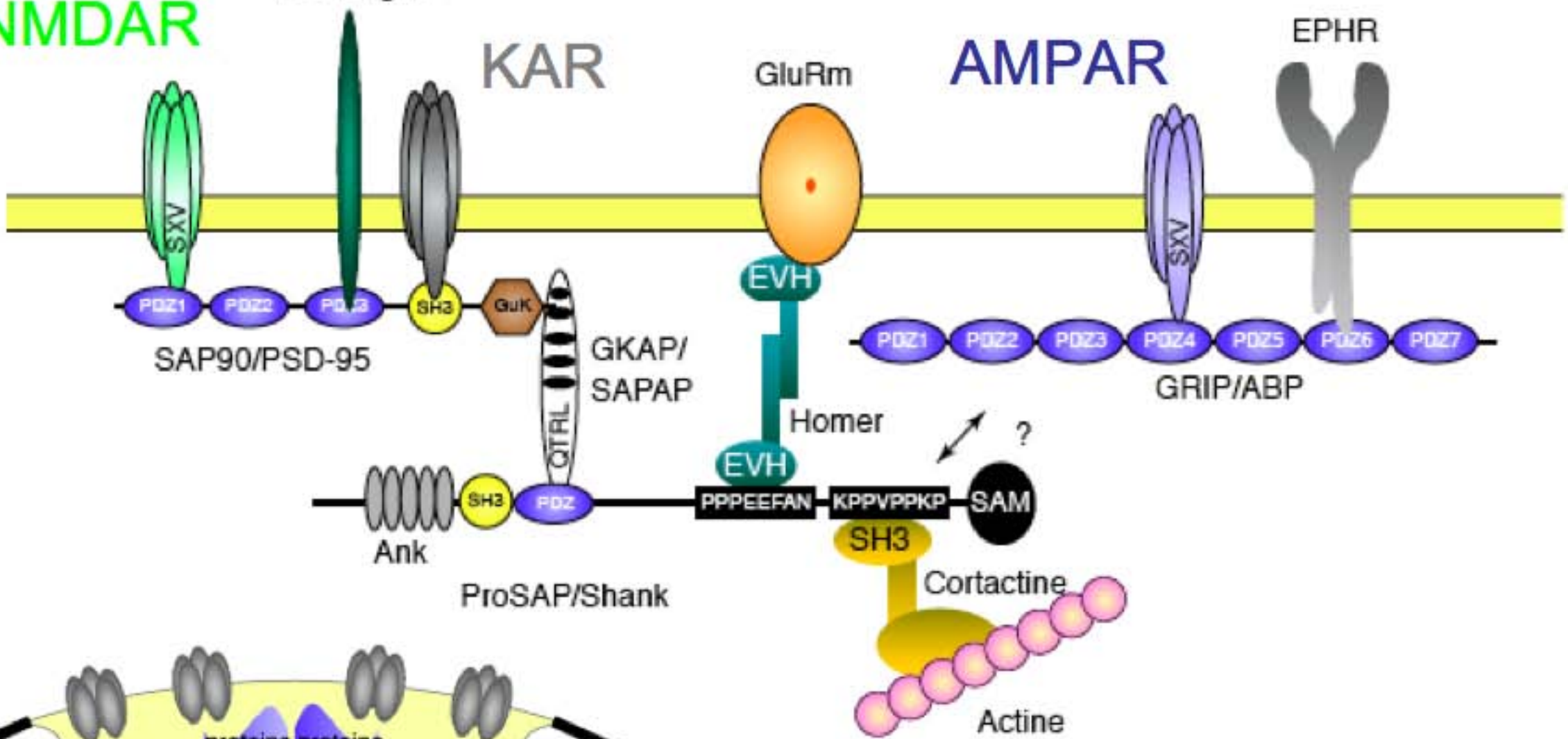
Neuroligine

KAR

GluRm

AMPA

EPHR

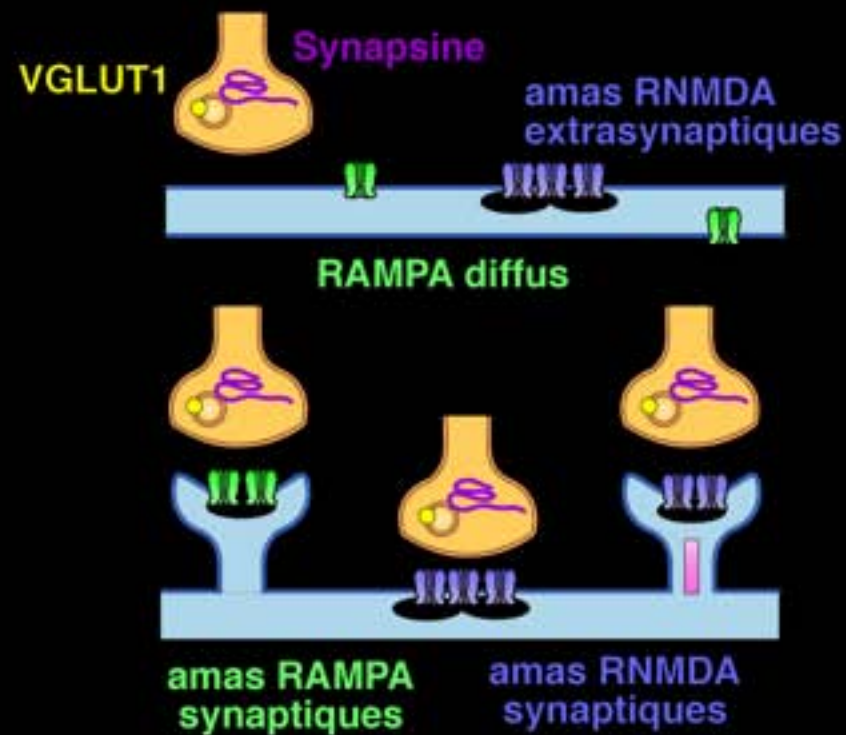


Targeting of post-synaptic proteins

Synapse excitatrice hippocampe

Laboratoire A.M. Craig

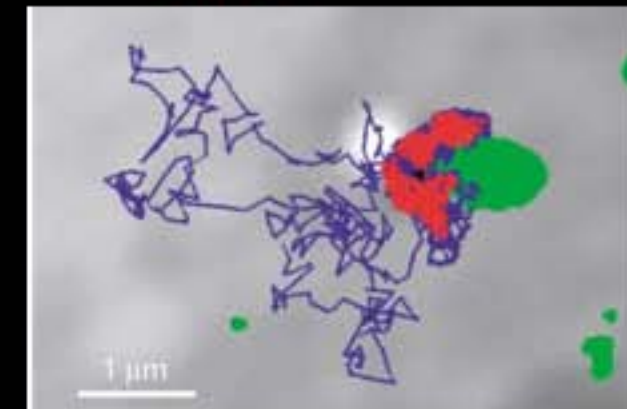
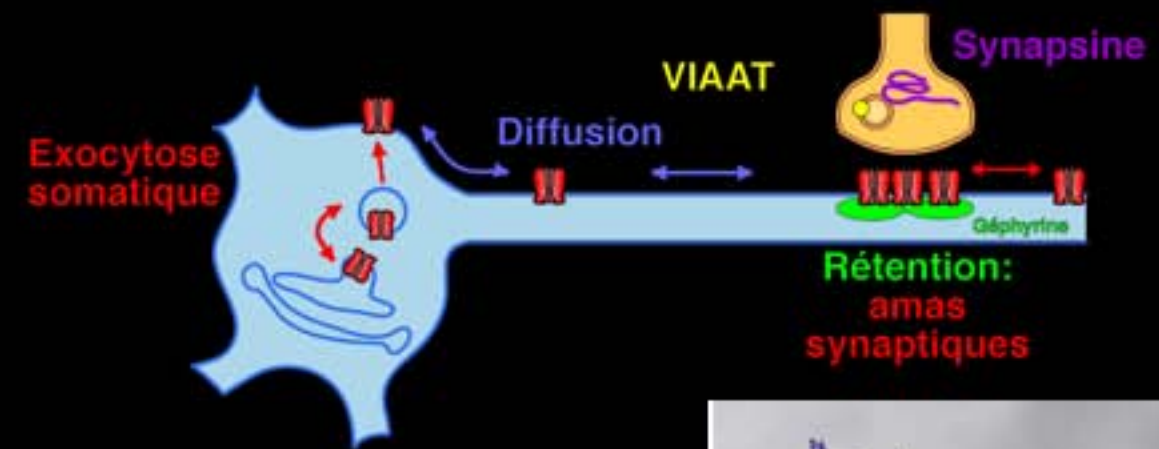
Rao et al., J. Neurosci., 2000
Rao et al., J. Neurosci., 2000



Synapse inhibitrice moelle épinière

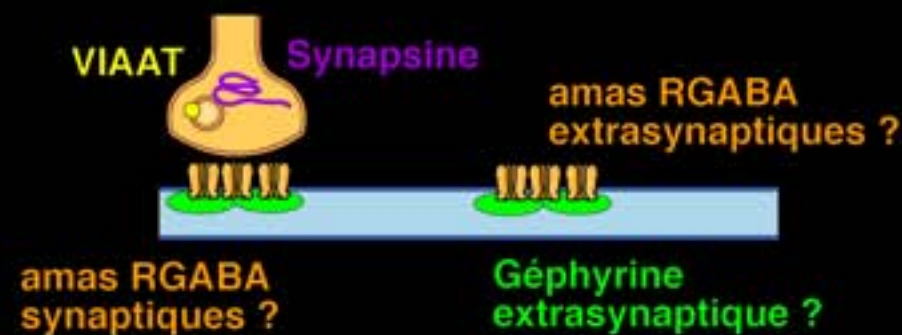
Laboratoire A. Triller

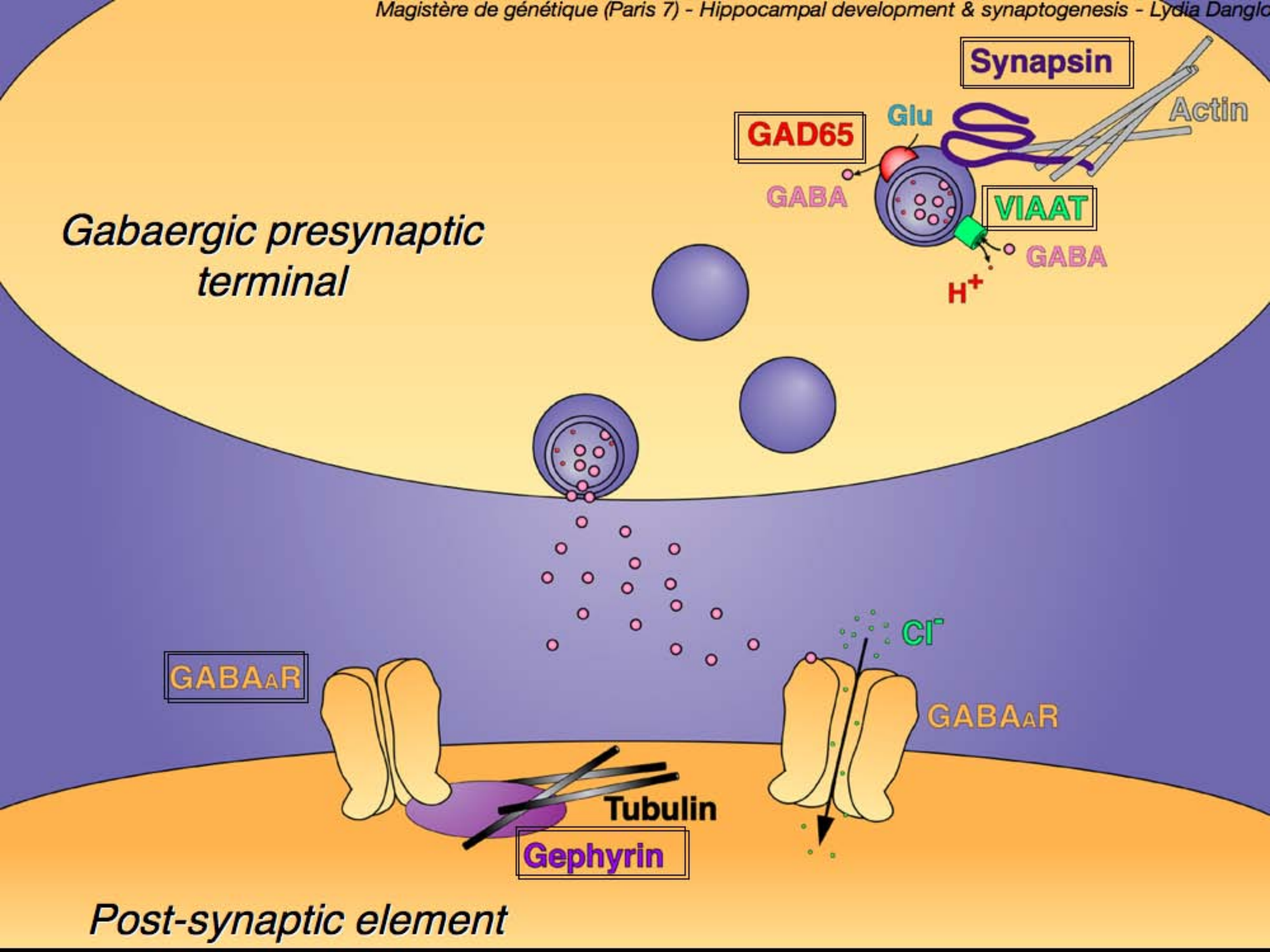
Rosenberg et al., J. Neurosci., 2000
Meier et al., JCS, 2000
Meier et al., Nat. Neur., 2001



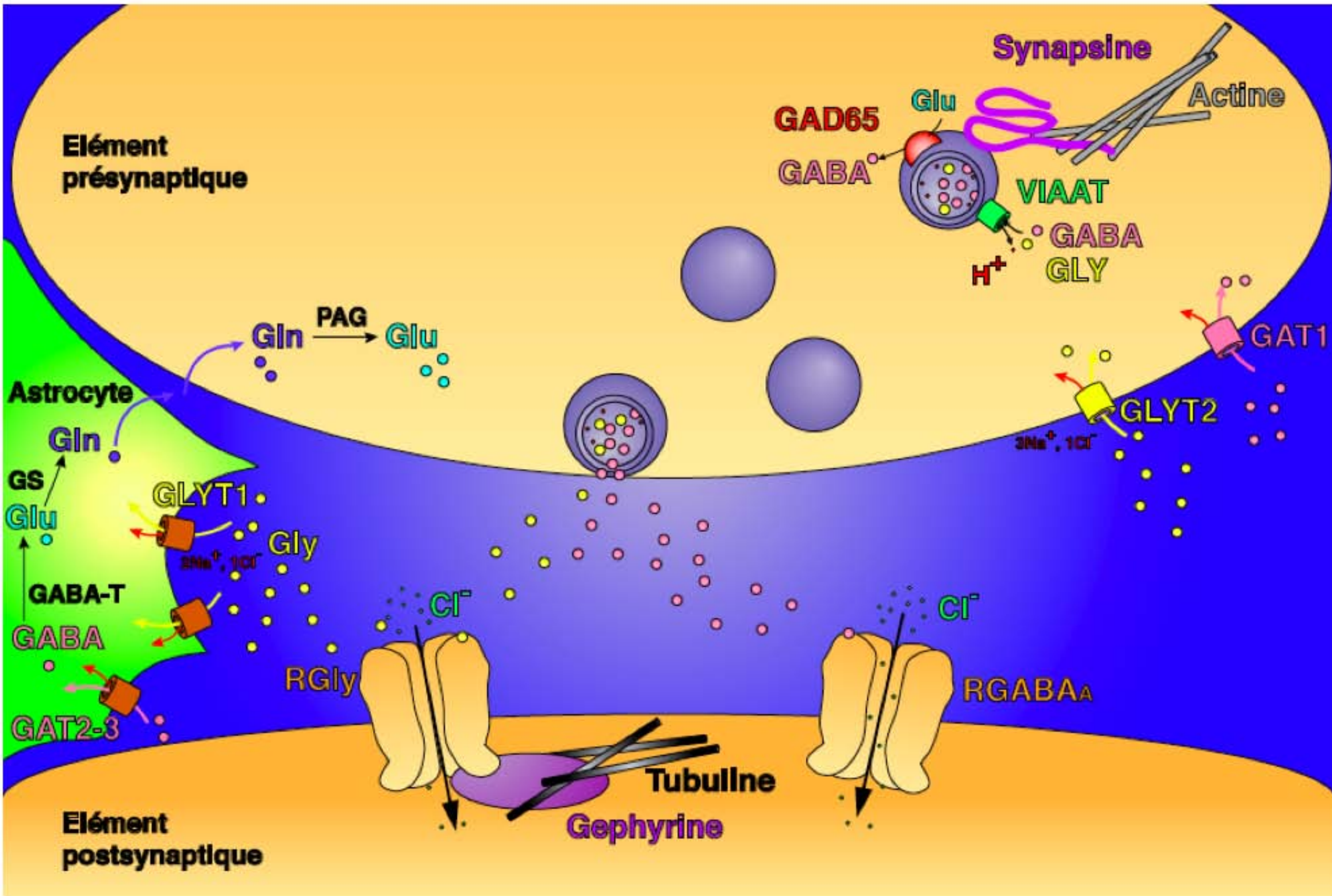
Synapse inhibitrice hippocampe

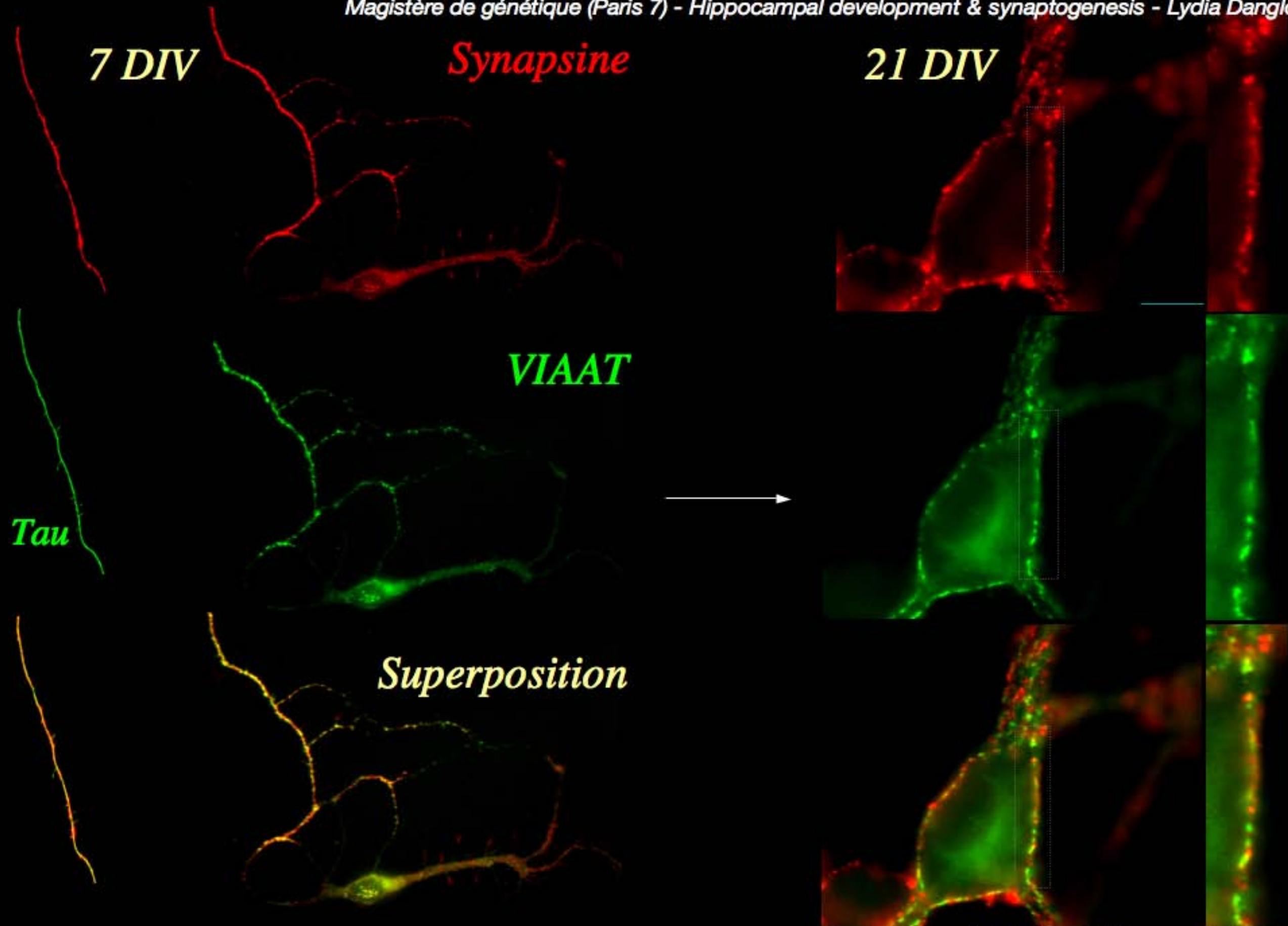
?





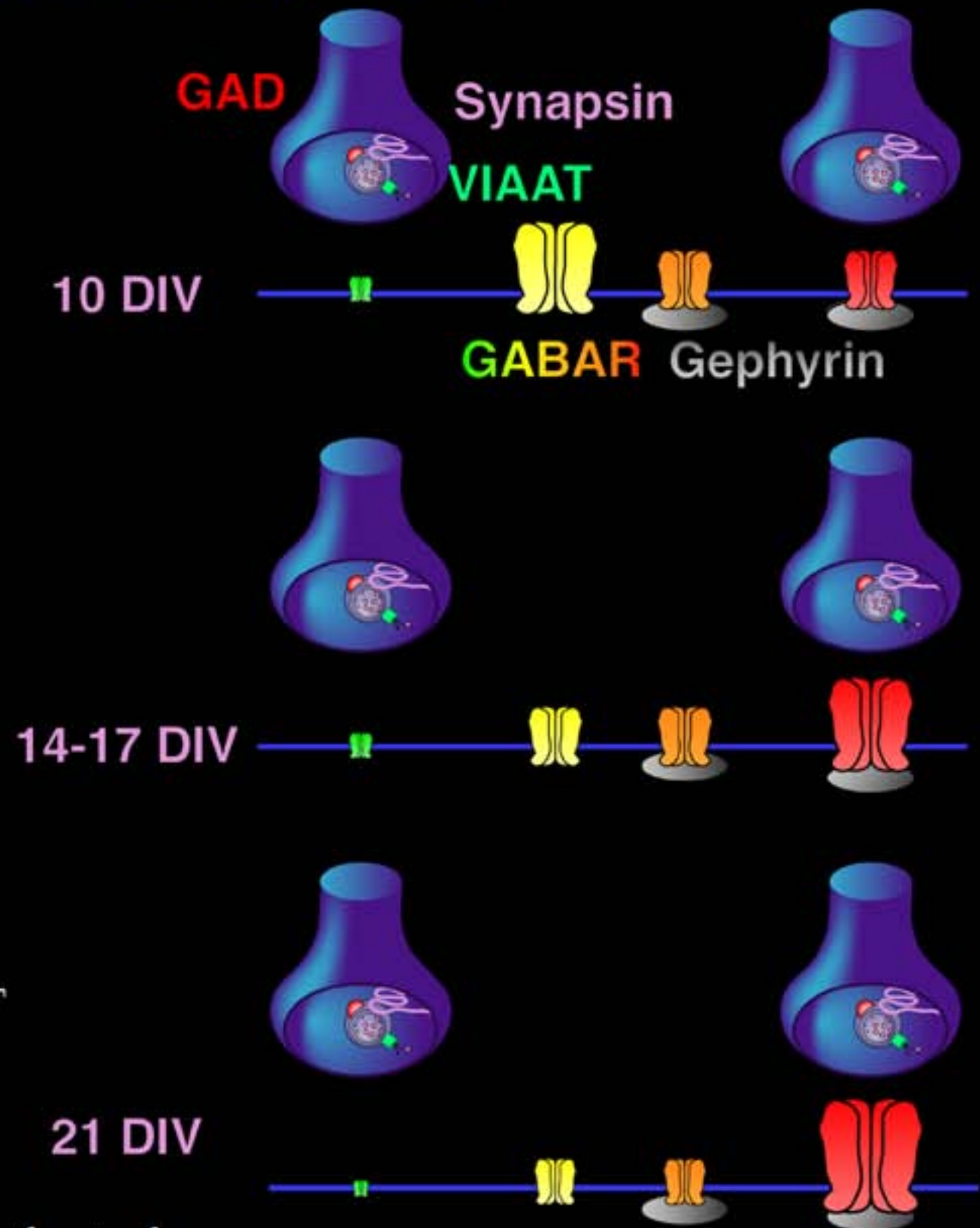
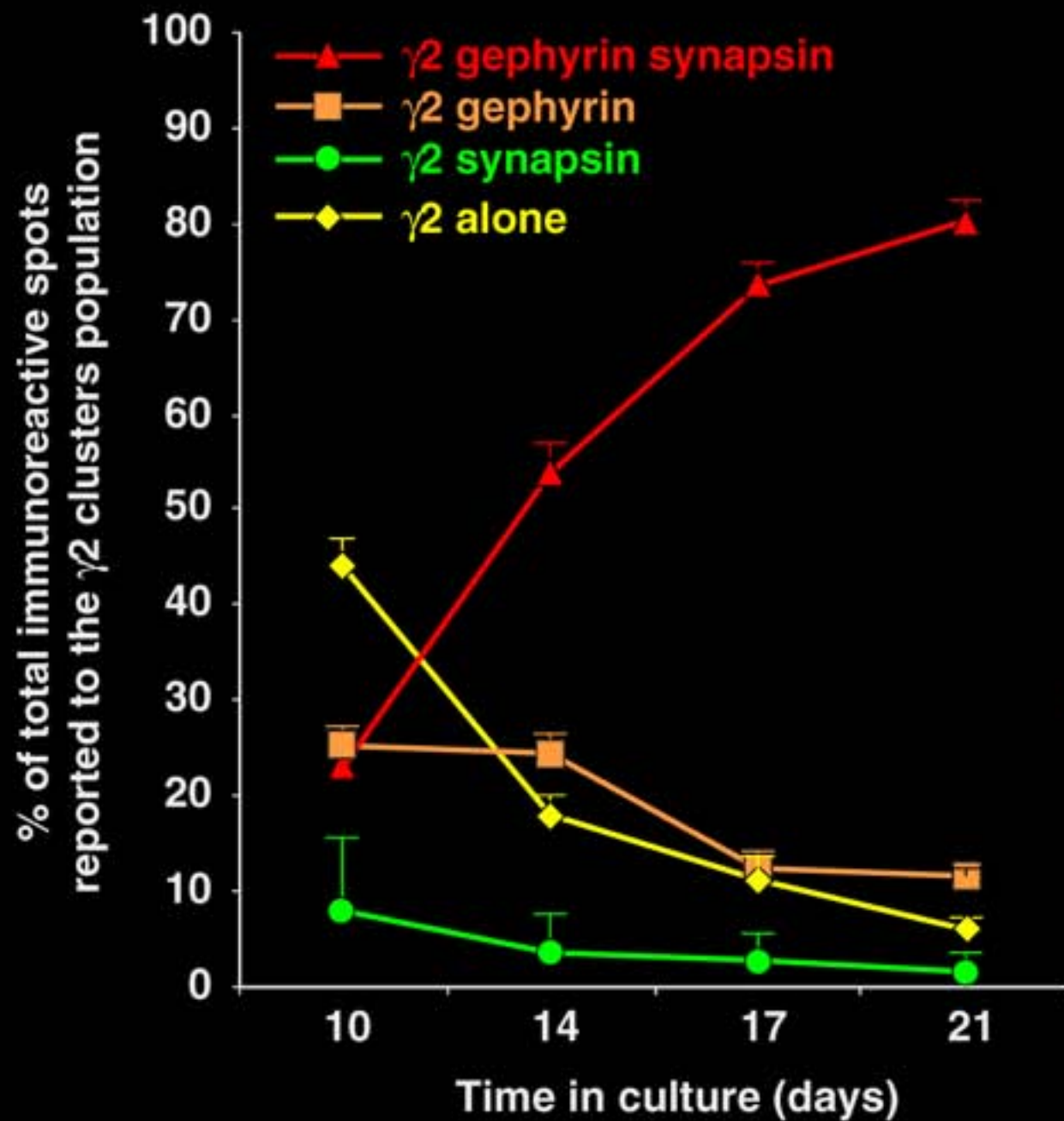
GABAergic synapse





VIAAT: Axonal diffuse expression and clustering after 10 days in vitro (DIV).

Gephyrin and GABAAR $\gamma 2$ associates before being detected at synapses



Gephyrin is dispensable for GABAAR $\gamma 2$ clustering.

Danglot et al. Mol cell Neurosci. (2003)

Synapses glutamatergiques

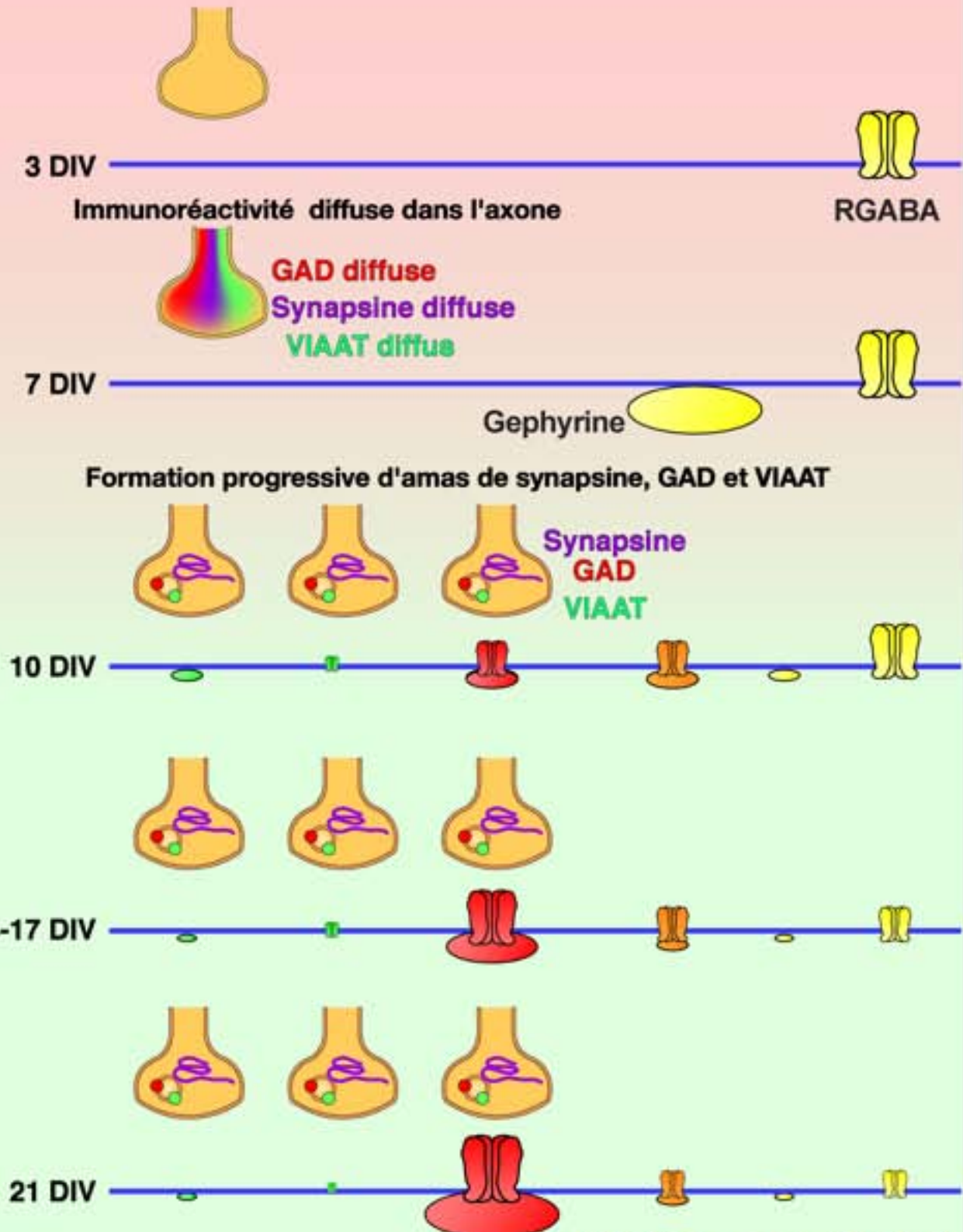
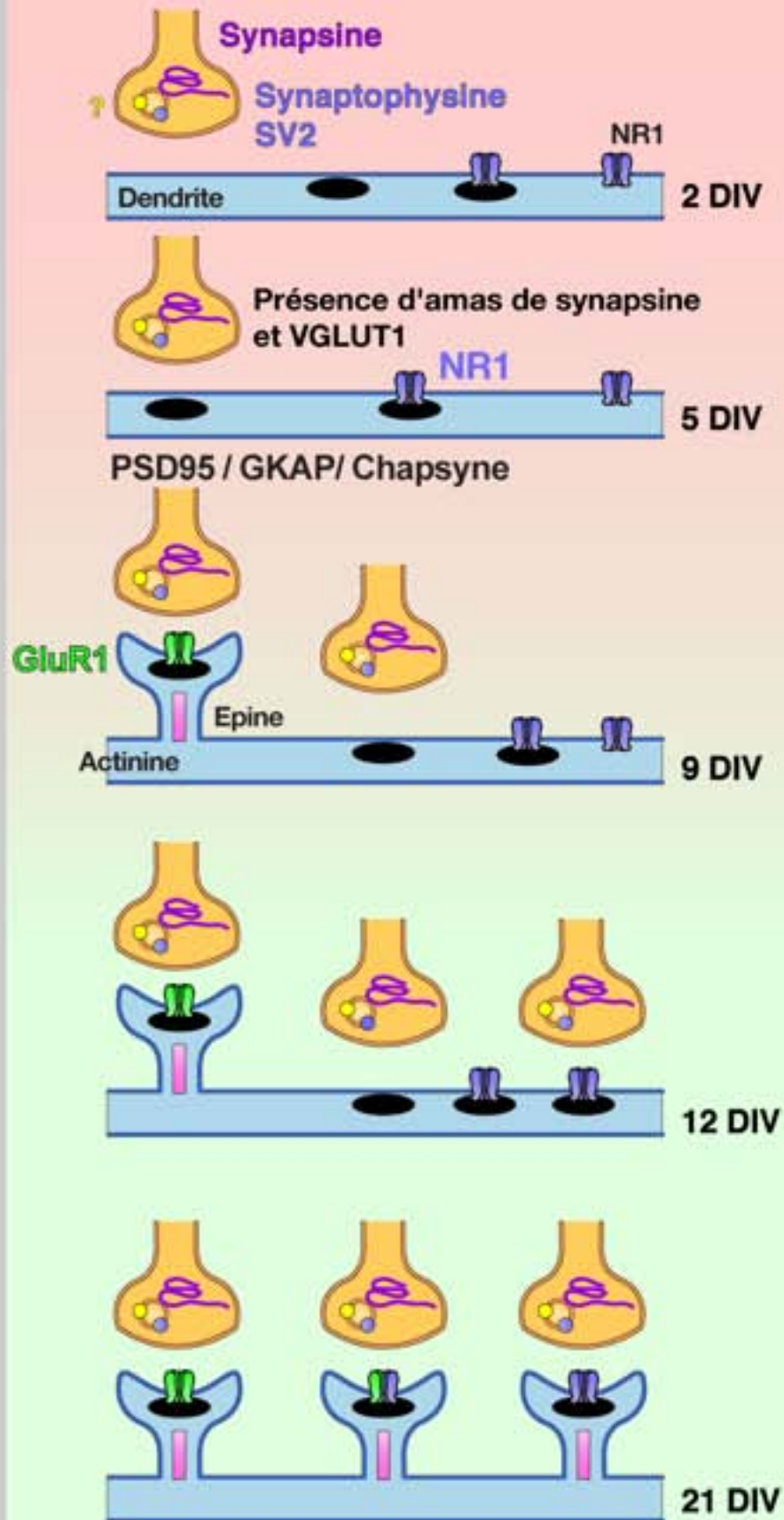
Synapses GABAergiques

Chlore dépolarisant

Chlore hyperpolarisant

GABA
exc.

GABA
inhib.



Hippocampal development & Synaptogenesis

1. Introduction to neuroanatomy

Neurulation

Differentiation : Forebrain-Midbrain-Hindbrain

Major structures of the brain

2. Hippocampus & the limbic system

Localization in human and rodents

General function

Connections and cellular populations

3. Formation of the hippocampus and dentate gyrus

Migration of excitatory neurons

pyramidal cells & granule cells

Migration of inhibitory interneurons

4. Dissociated hippocampal neurons in culture

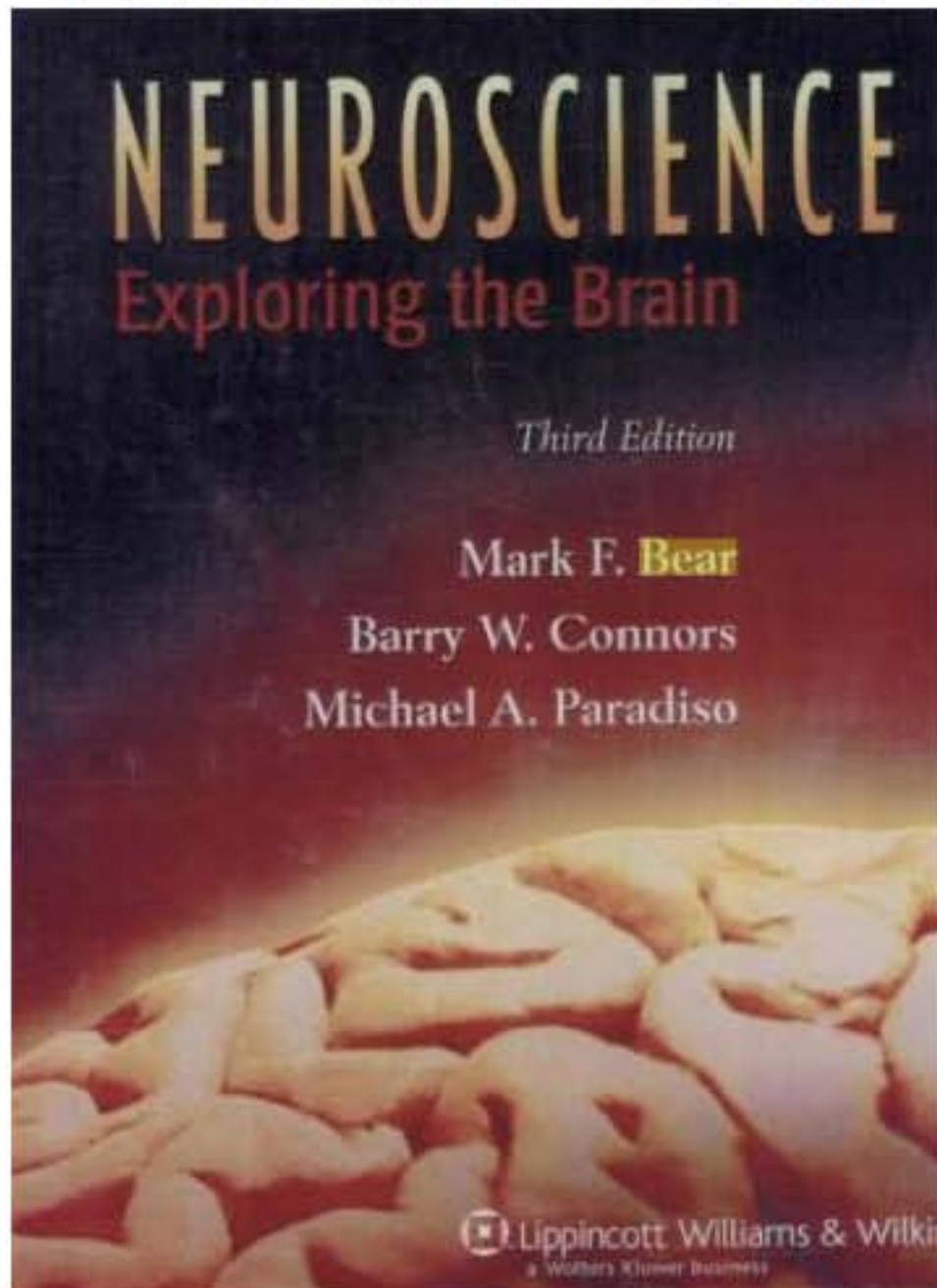
The sandwich model of Gary Banker

Acquisition of neuronal polarity

Synaptogenesis

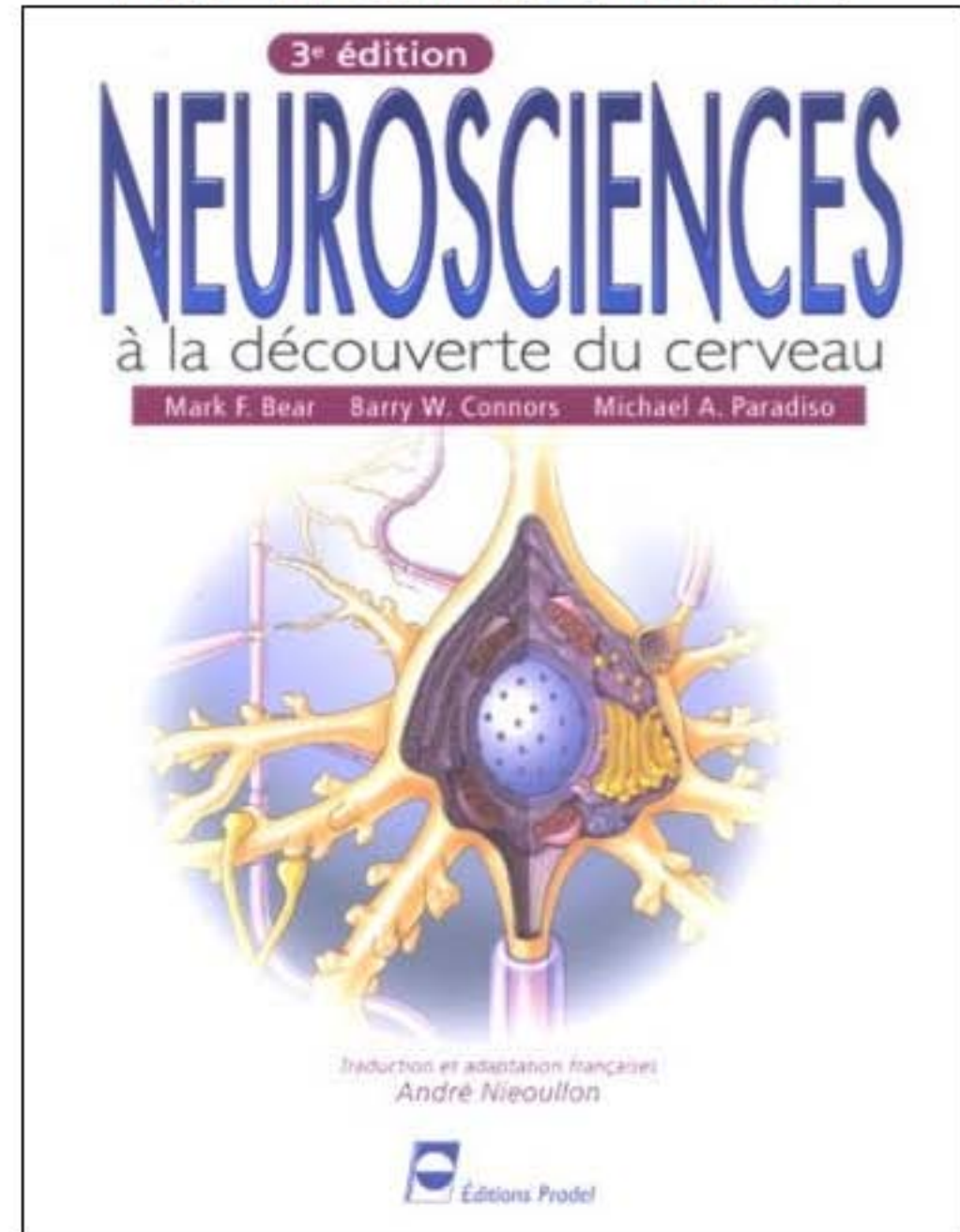
Some interesting handbooks ...

ENGLISH VERSION



Neuroscience: Exploring the Brain
de Mark F. Bear, Barry W. Connors, Michael A. Paradiso
2006 - 857 pages
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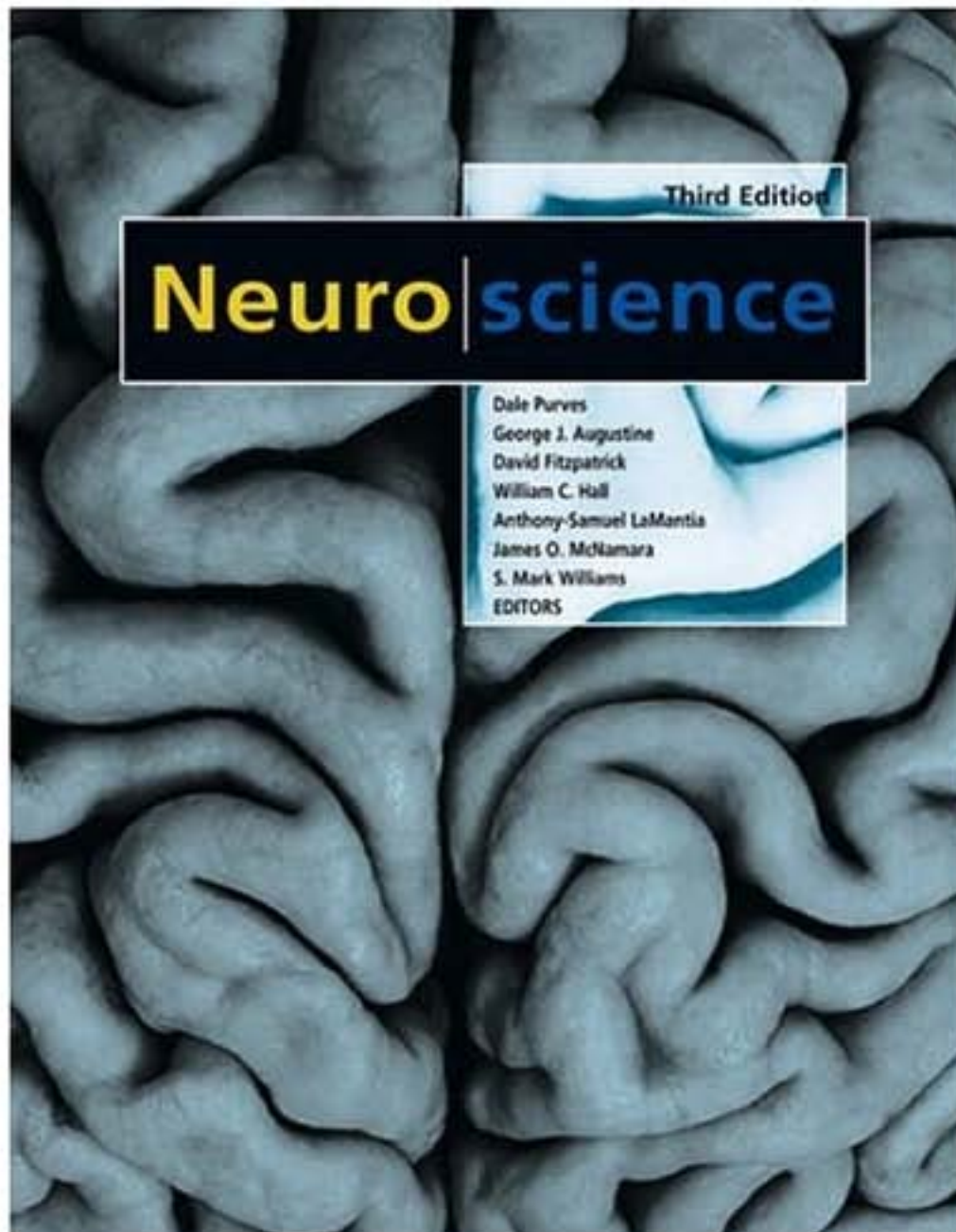
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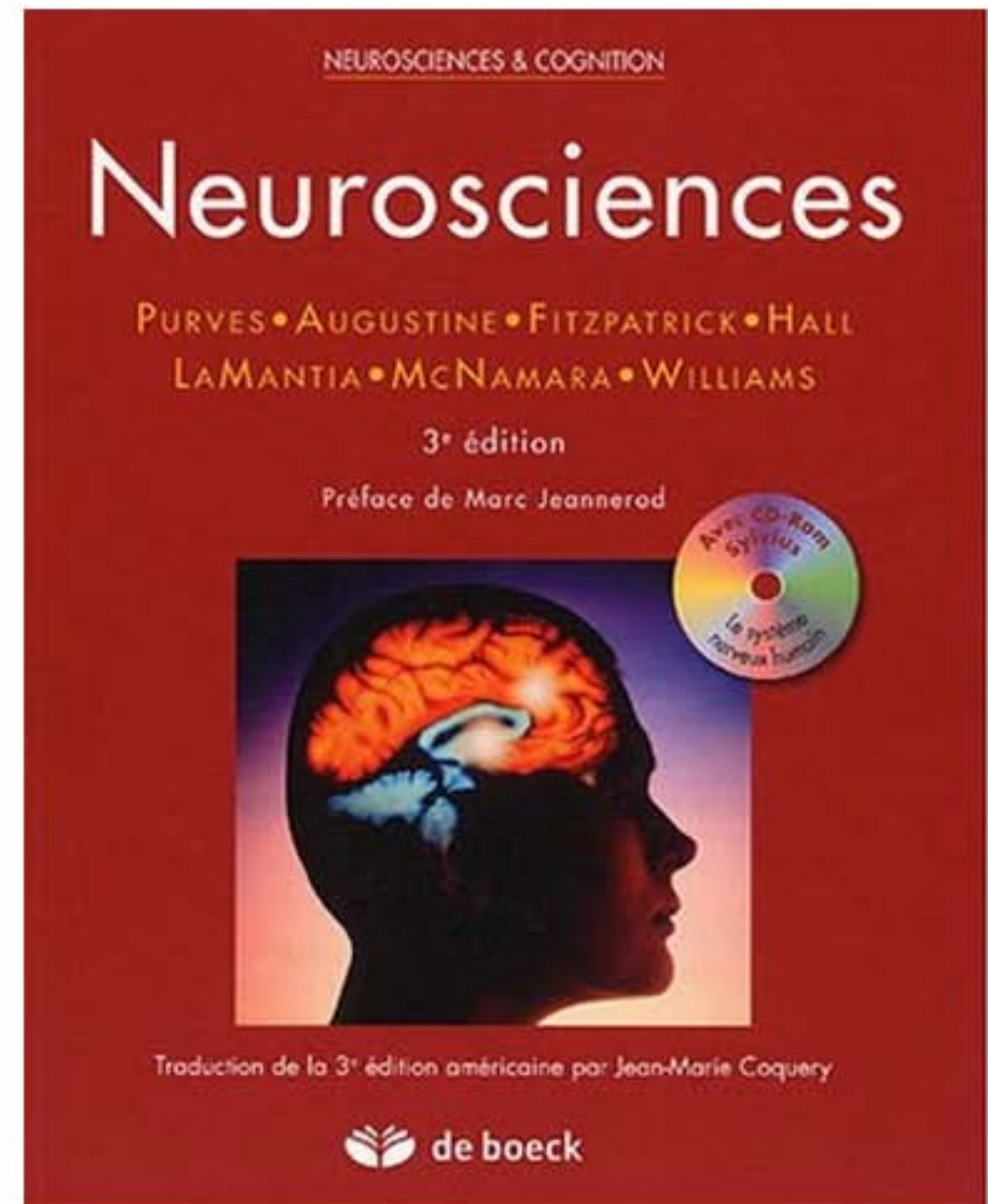


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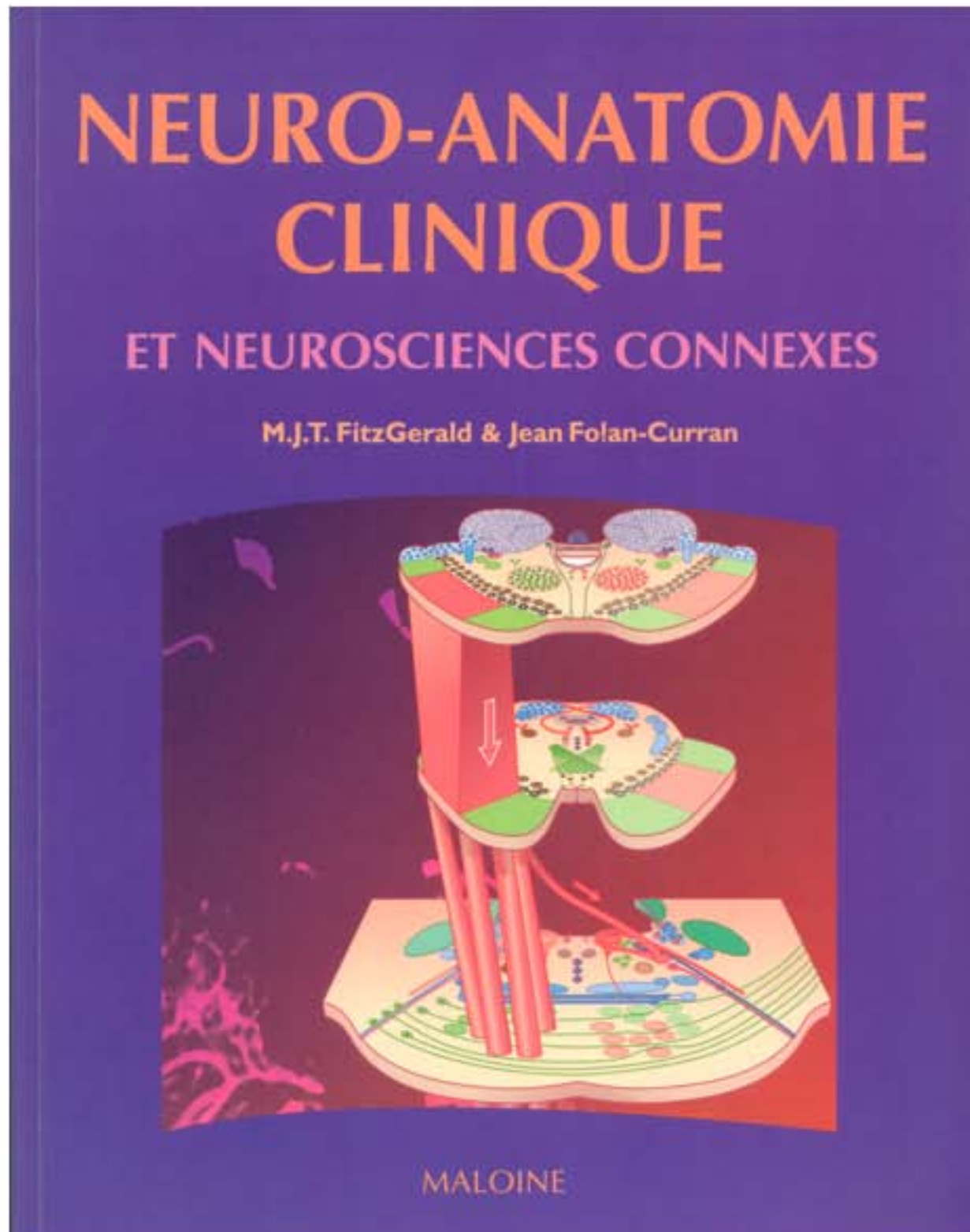
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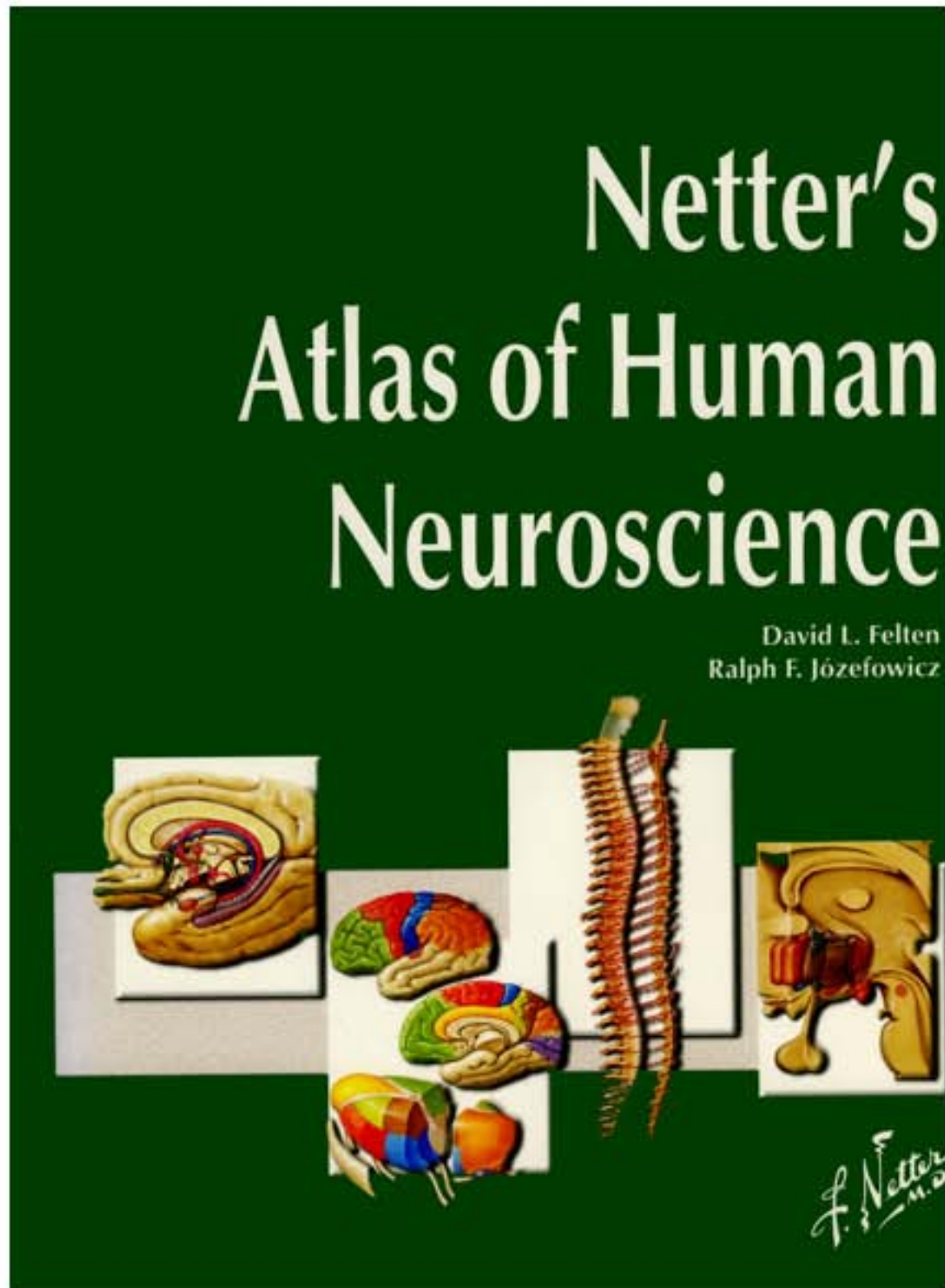
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