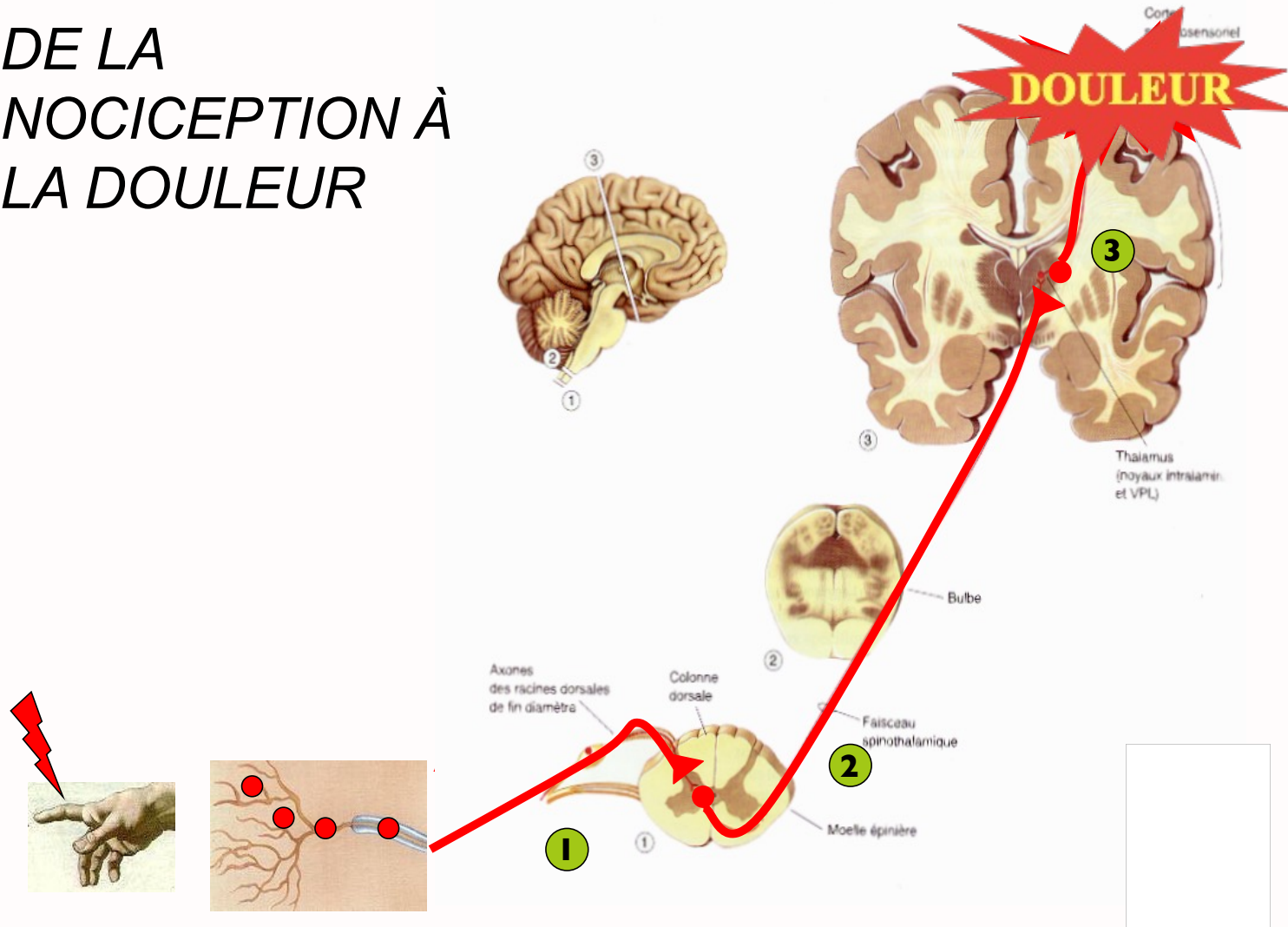




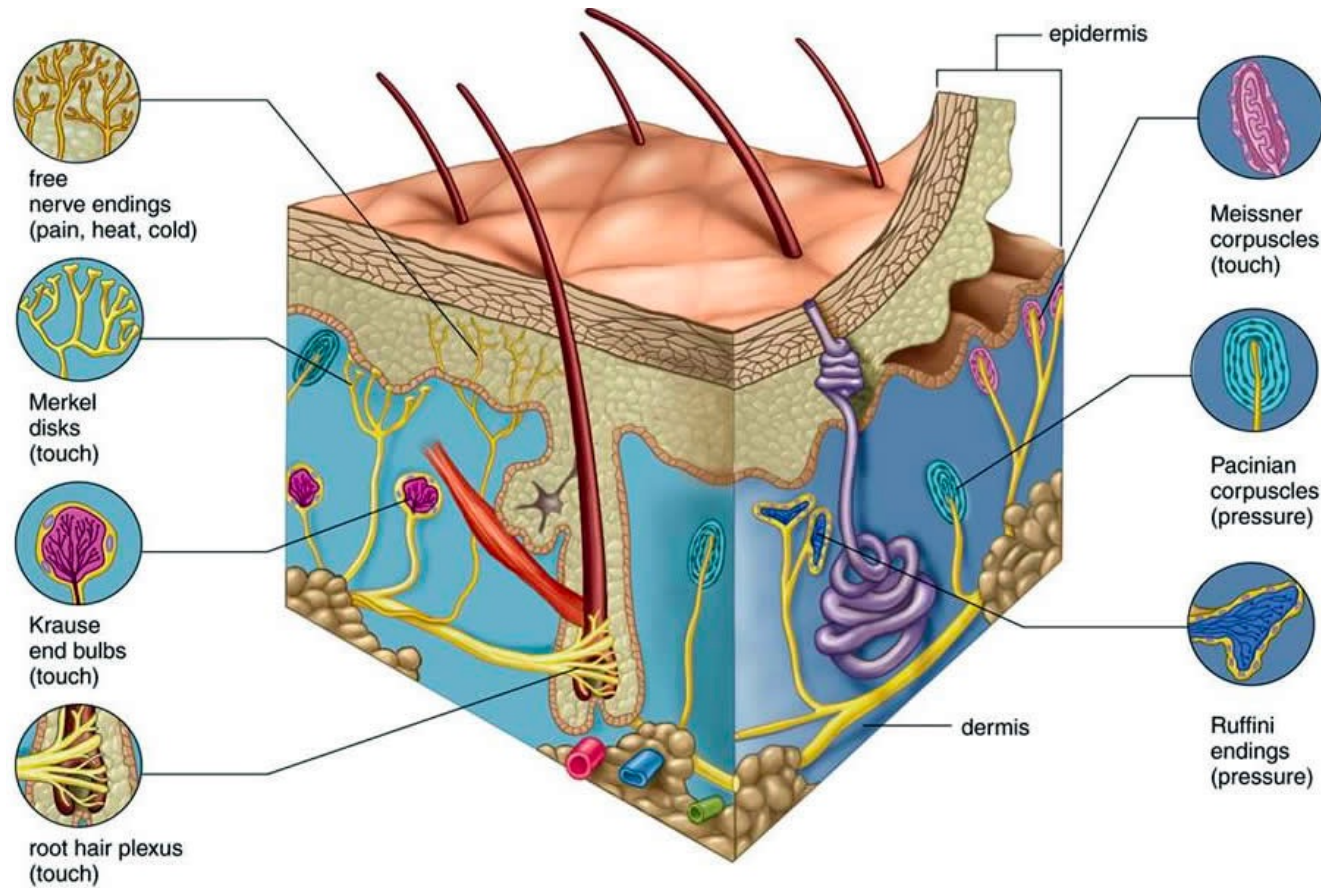
MMD 8800



DE LA NOCICEPTION À LA DOULEUR



Récepteurs cutanés



<http://biologyboom.com/write-a-note-on-mechanoreceptors-tactile-receptors-in-the-skin/>

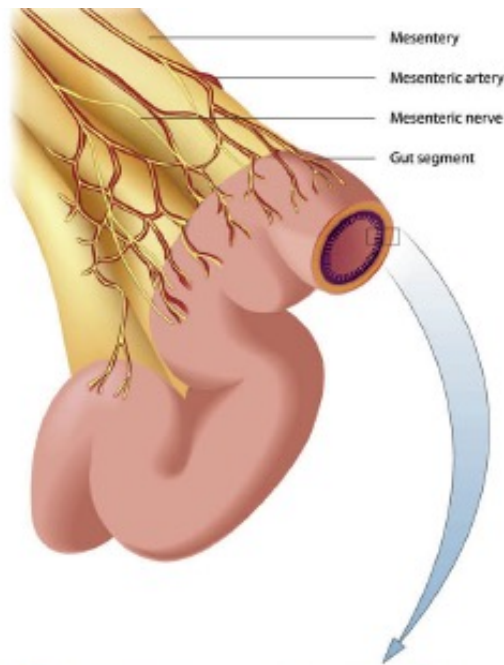


Review

Basic and clinical aspects of gastrointestinal pain

Charles H. Knowles^{a,*}, Qasim Aziz^b

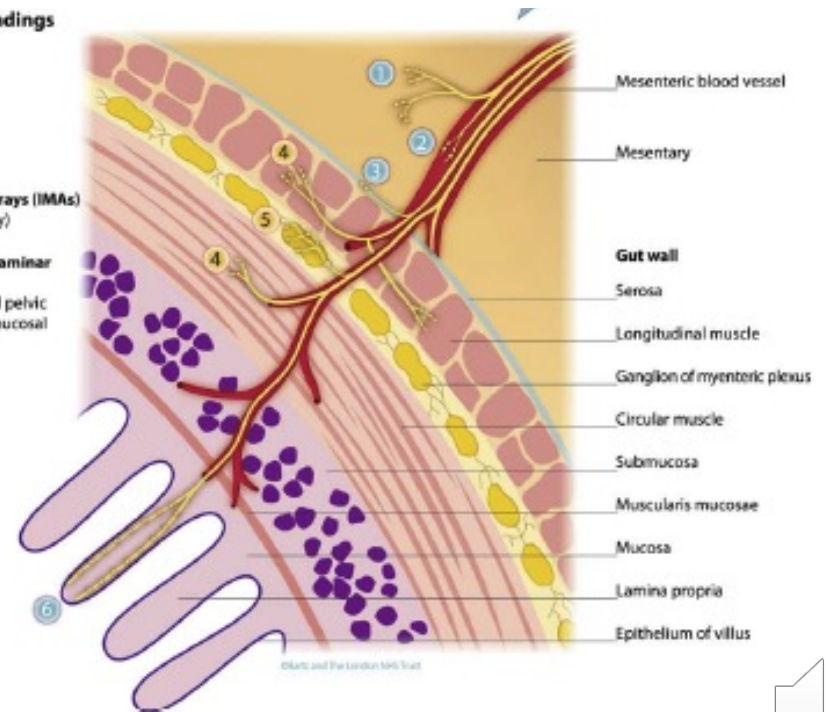
Anatomy of visceral nociception



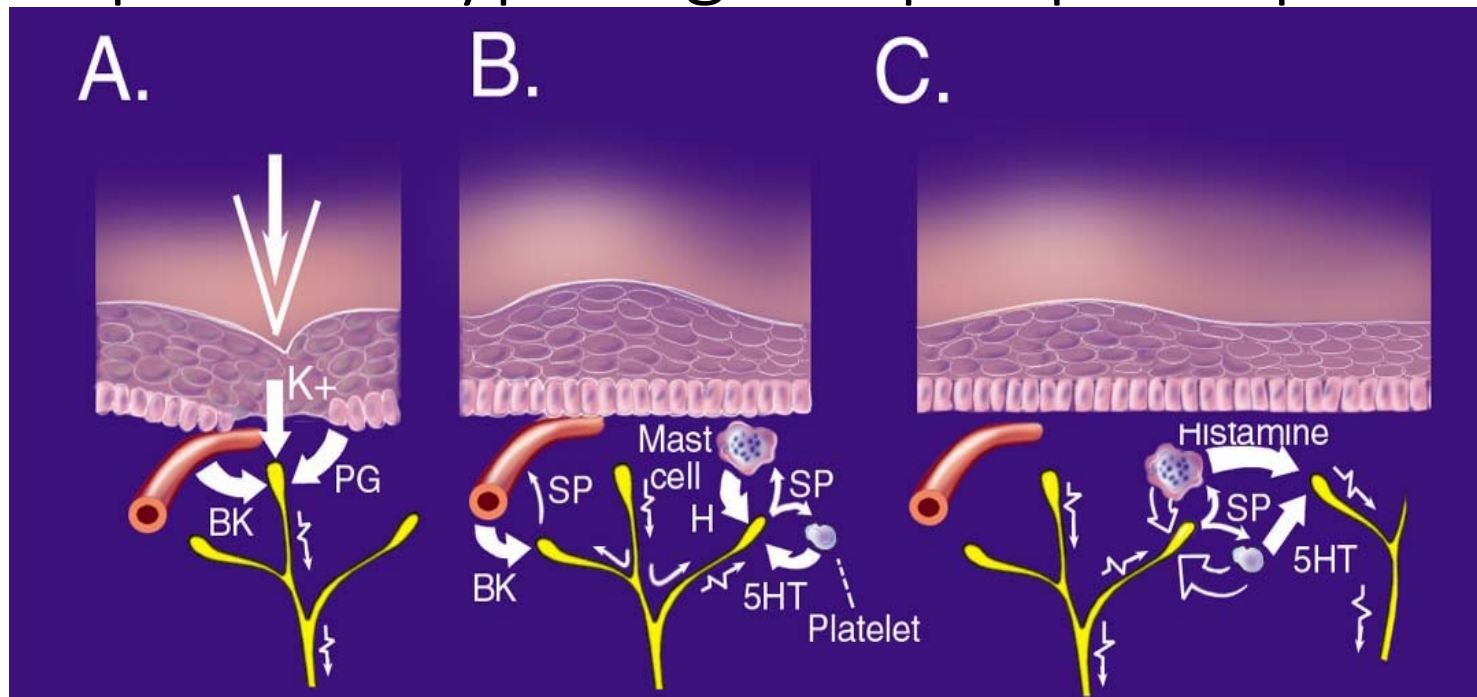
Afferent nerve endings

Afferent nerve endings

- ① Mesenteric
- ② Perivascular
- ③ Serosal
- ④ Intramuscular arrays (IMAs) (vagus nerves only)
- ⑤ Intraganglionic laminar endings (IGLEs) (IGLEs - vagus and pelvic nerves only; submucosal IGLEs not shown)
- ⑥ Mucosal
- ⑦ Probable main contributors to nociception



Nocicepteurs: Hyperalgésie périphérique



Terminaisons nerveuses libres



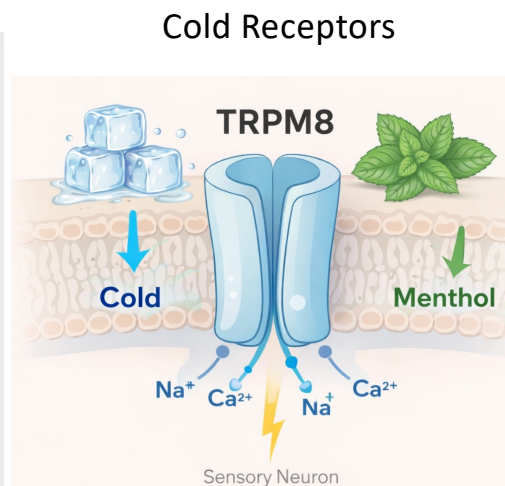
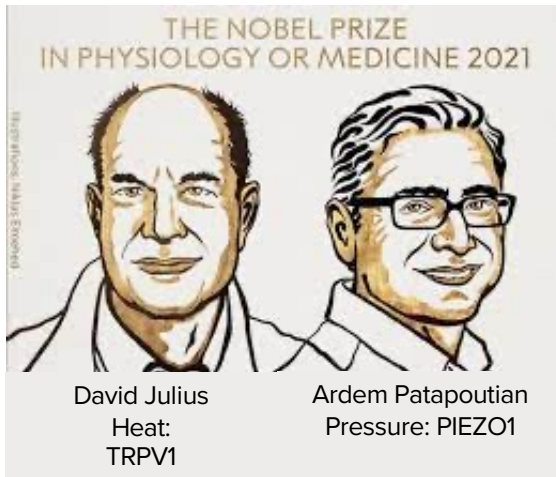
Inflammation and Nociception Mediators

Primary Inflammatory Mediators	Pro-Inflammatory Cytokines	Neurotrophic Factor	Neuropeptides Released by Sensory Nerve
Bradykinins: Pro-inflammatory peptides → Directly activate nociceptors (B1 and B2 chronic inflammation). → Produce peripheral sensitization.	TNF-α: Tumor Necrosis Factor - alpha → Upregulates COX-2 → Promotes peripheral sensitization.	NGF (Nerve Growth Factor): → Produced by fibroblasts, mast cells, immune cells. → Increases expression of nociceptive ion channels → Induces B1 receptor expression → Strong driver of peripheral sensitization	Substance P : → Vasodilation → Plasma extravasation → Amplifies neurogenic inflammation.
Prostaglandins (PGs): → Synthesized via COX-2 from arachidonic acid. → Lower the activation threshold of nociceptors (key sensitizers).	IL-1: Interleukin-1 → Amplifies inflammatory response. → Increases prostaglandin production → Facilitates hyperalgesia.		CGRP (Calcitonin Gene-Related Peptide) Potent vasodilator. → Contributes to local hyperemia (more blood in the vascular system) → Important in inflammatory pain.
Histamine: → Released by mast cells. → Vasodilation → Increased vascular permeability → Contributes to pain and itch.	IL-6: Interleukin-6 → Dual pro- and anti-inflammatory roles. → peripheral sensitization, potential role in central pain sensitization.		COX-2: Inducible enzyme producing prostaglandins. → Major pharmacological target (NSAIDs and COX-2 inhibitors). Upregulated in chronic inflammation. → Increases tissue responsiveness to bradykinins.
5-HT (Serotonin) → Released primarily from platelets. → Can activate or modulate nociceptors depending on receptor subtype. → Contributes to inflammatory hyperalgesia.	IL-8 : Interleukin-8 → Chemokine → Recruits immune cells → Maintains local inflammation.		
H⁺: hydrogen ion (Local acidosis): → Tissue acidification during inflammation. → Activates ASIC and TRPV1 channels → Major contributor to inflammatory pain.	ASICs: Acid-sensing ion channels TRPV1: Transient Receptor Potential Vanilloid 1 (heat) B1 and B2 : Bradykinin receptors		

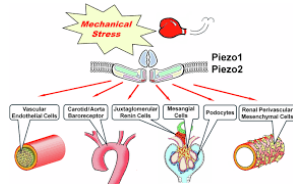


Cellular and Molecular Mechanisms of Pain

Allan I. Basbaum,^{1,*} Diana M. Bautista,² Grégory Scherrer,¹ and David Julius^{3,*}



HOT



Pressure

Cold

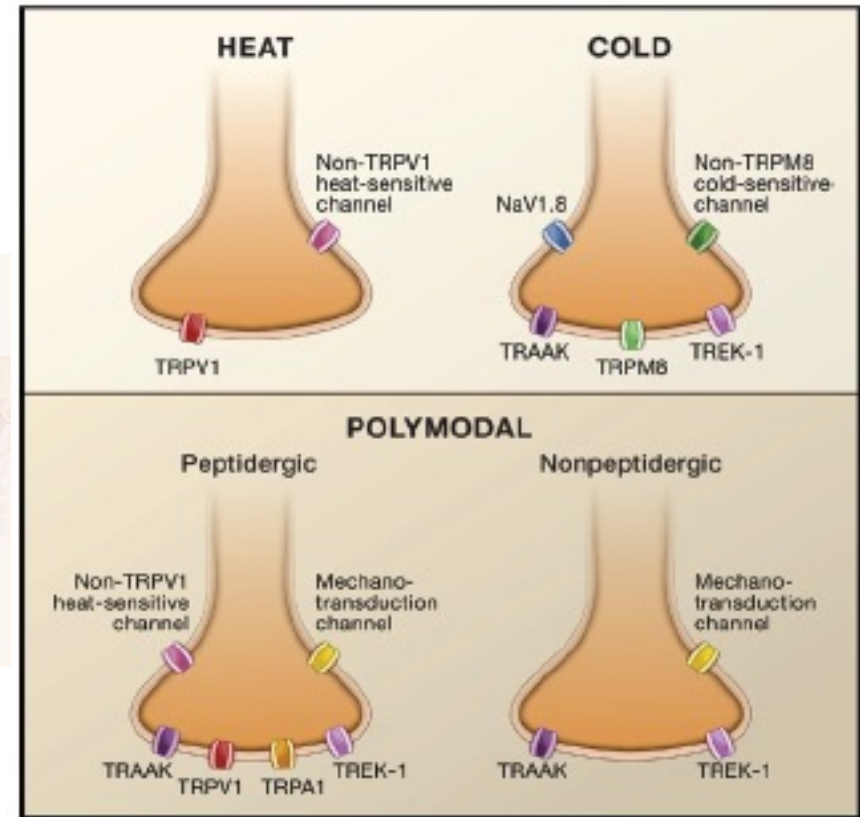


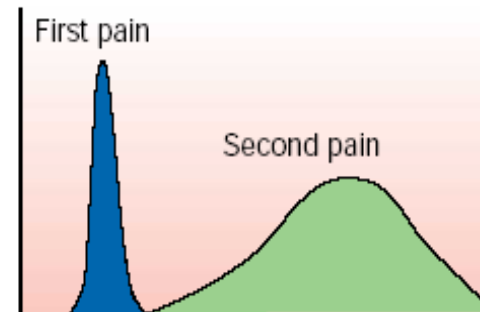
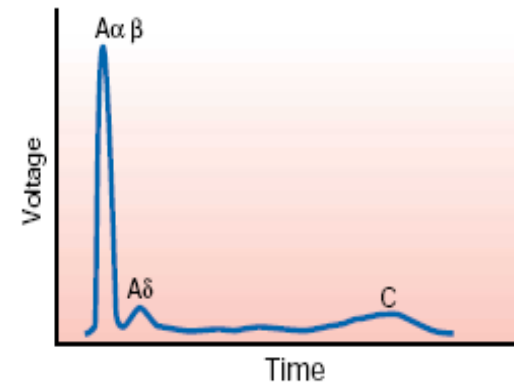
Figure 3. Nociceptor Diversity

There are a variety of nociceptor subtypes that express unique repertoires of transduction molecules and detect one or more stimulus modalities.

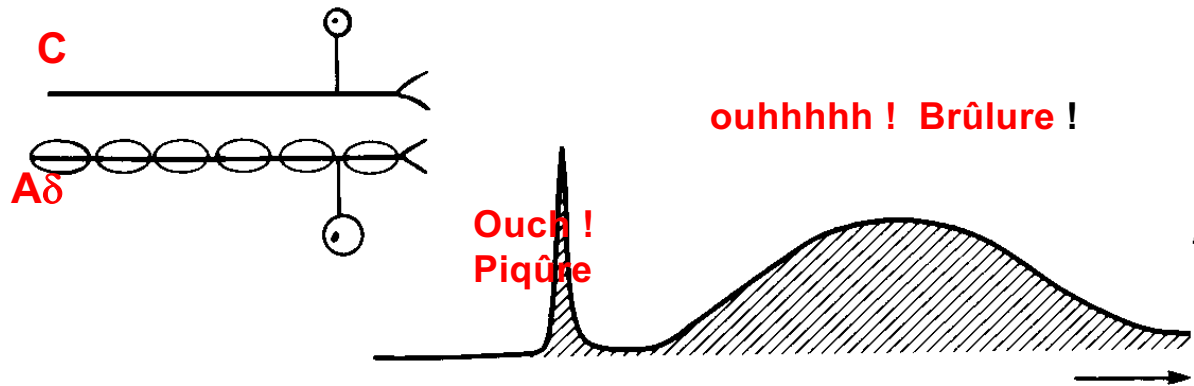


Fibres de la nociception

Primary afferent axons		
	Aα and Aβ fibres	Thermal threshold
	Myelinated Large diameter Proprioception, light touch	None
	Aδ Fibre	
	Lightly myelinated Medium diameter Nociception (mechanical, thermal, chemical)	~ 53 °C Type I ~ 43 °C Type II
	C fibre	
	Unmyelinated Small diameter Innocuous temperature, itch Nociception (mechanical, thermal, chemical)	~ 43 °C

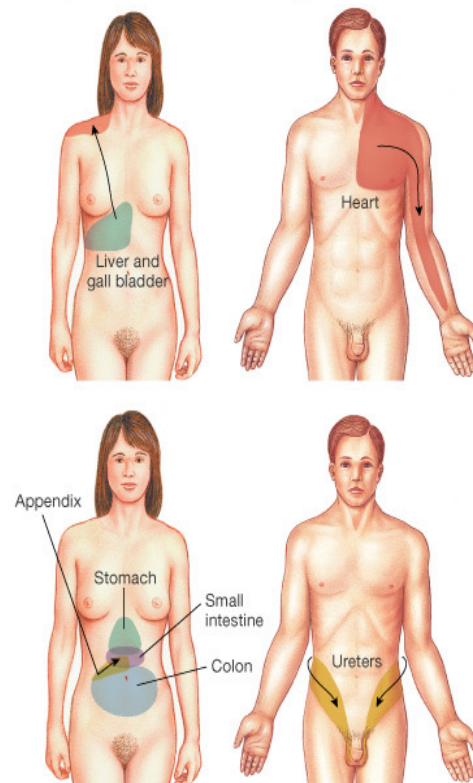


Première et seconde douleur

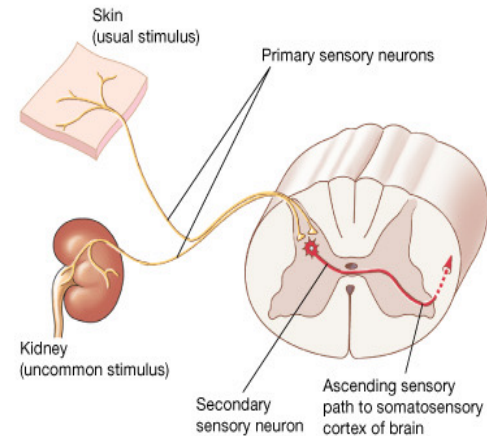


Douleur projetée : Viscéro-somatique

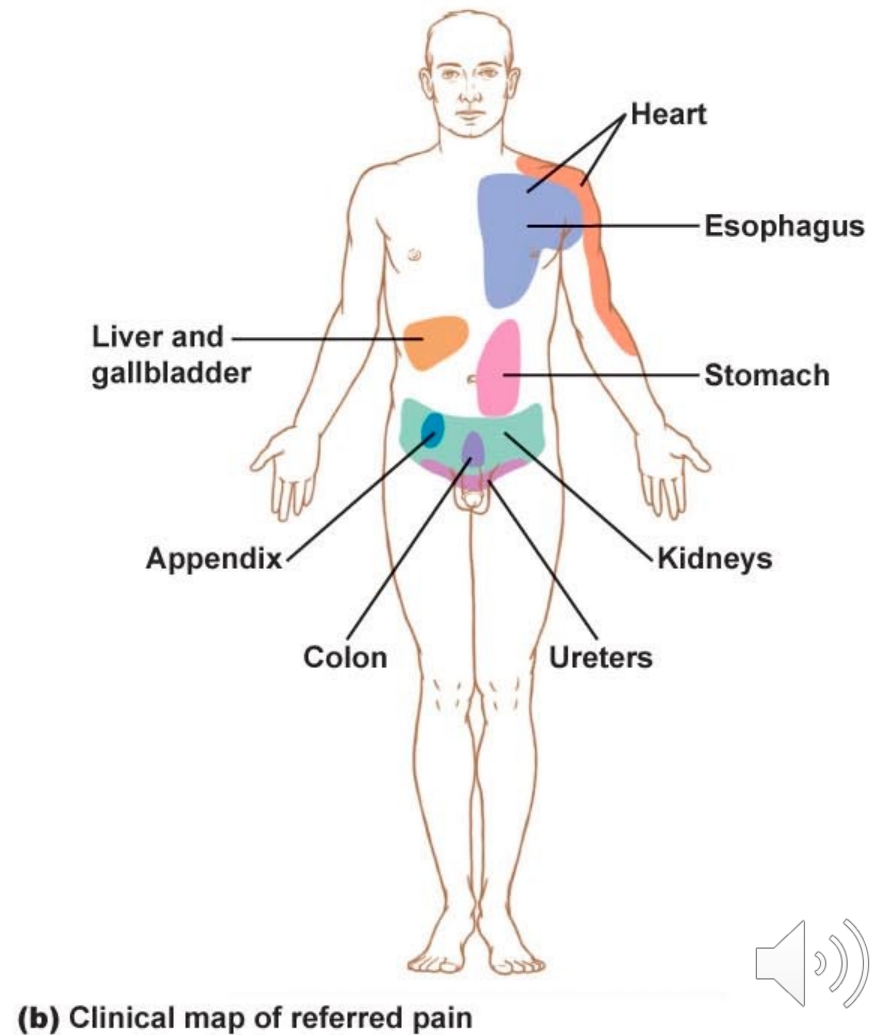
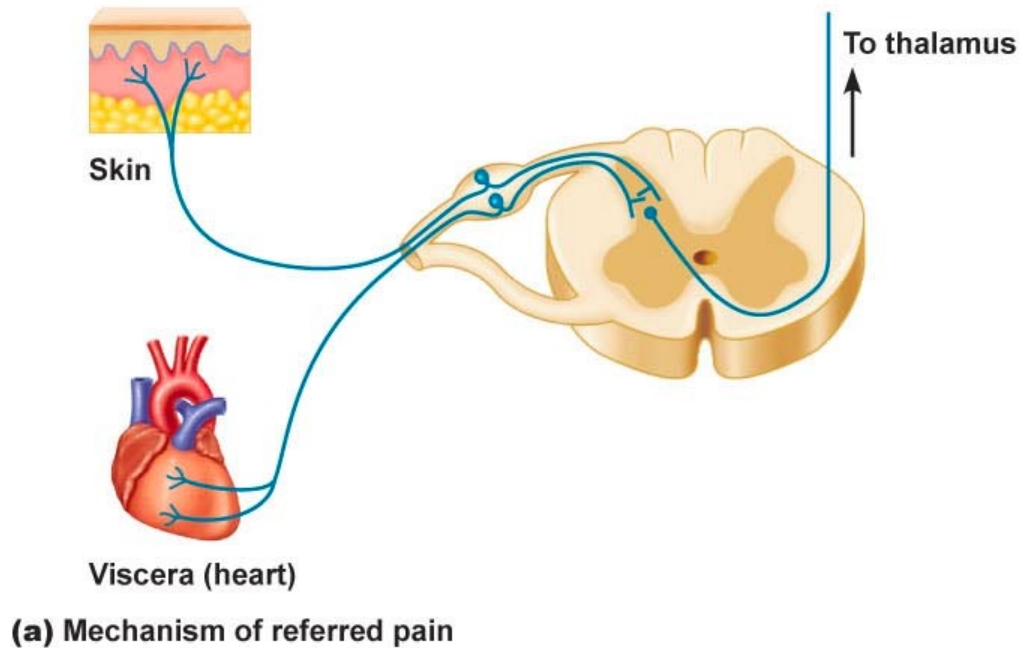
(a) Pain in internal organs is often sensed on the surface of the body, a sensation known as **referred pain**.



(b) One theory of referred pain says that nociceptors from several locations converge on a single ascending tract in the spinal cord. Pain signals from the skin are more common than pain from internal organs, and the brain associates activation of the pathway with pain in the skin. Adapted from H.L. Fields, *Pain* (McGraw Hill, 1987).

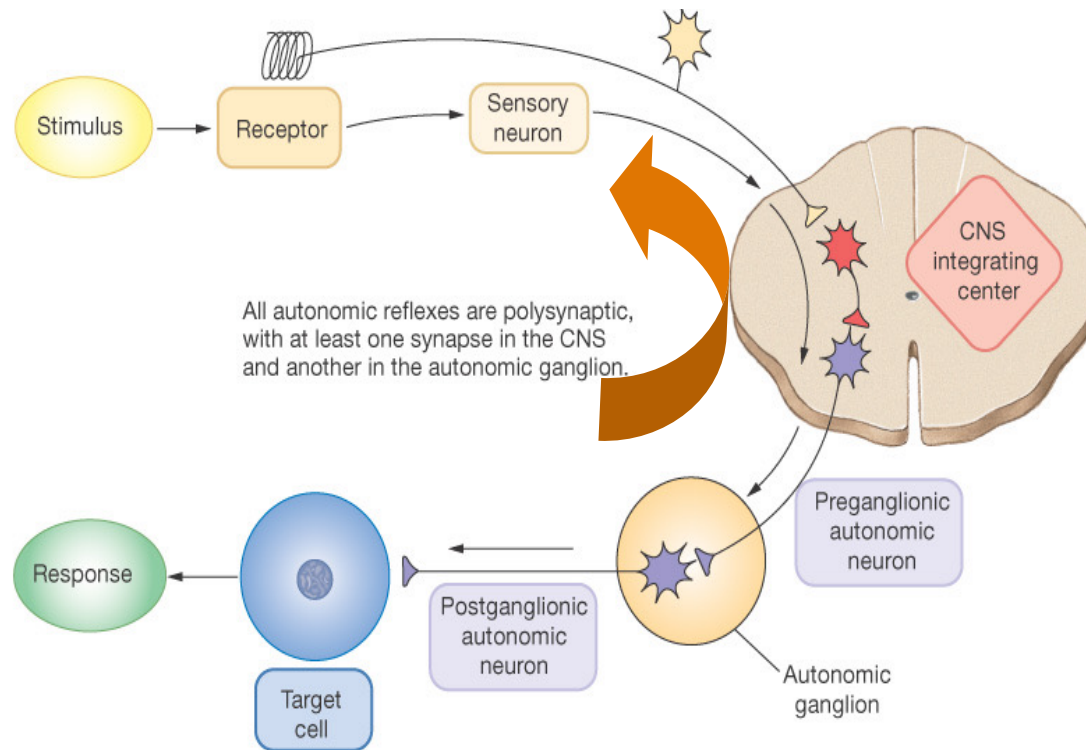


Douleur projetée



Réflexe somato-viscéral

Mais aussi viscéro-somatique



Can Quantitative Sensory Testing Move Us Closer to Mechanism-Based Pain Management?

Cruz-Almeida Y, Fillingim RB. *Pain Med*, (2013).



QST (Quantitative Sensory Testing) Périphérie

A β : Touch, vibration



A δ : Sharp Pain



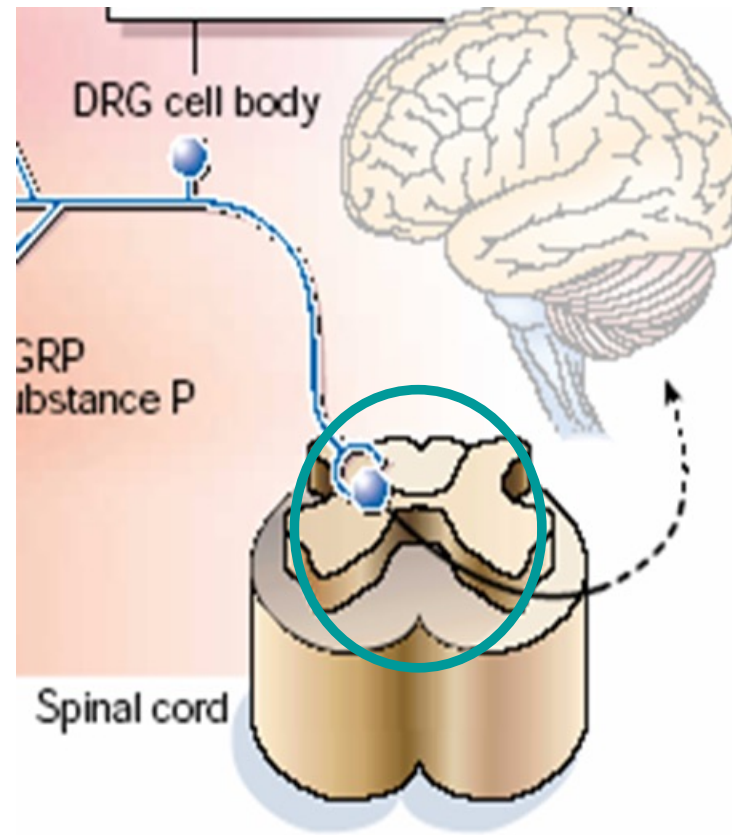
C: Heat



Mécanismes périphériques: Traitements



Nocicepteurs secondaires – cornes postérieures de la moelle

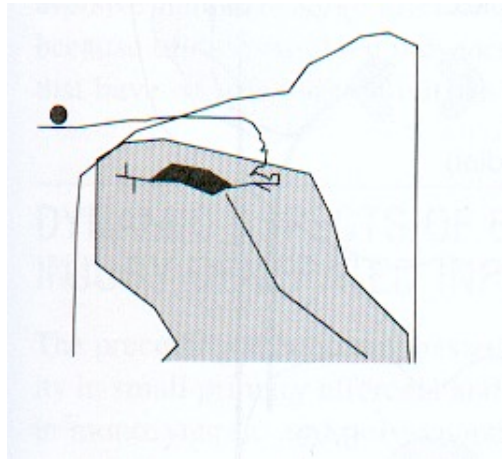


Neurones nociceptifs

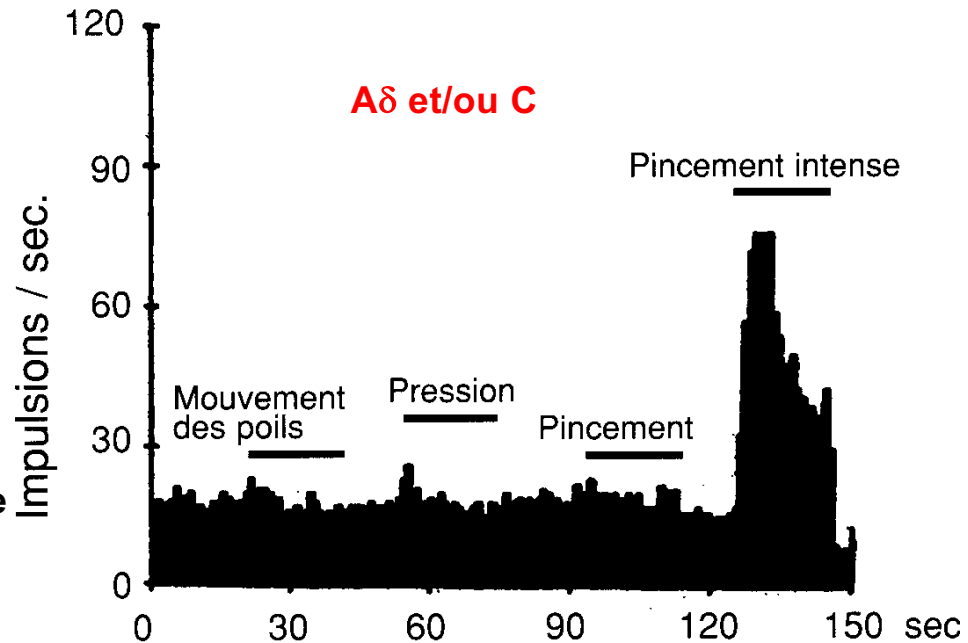
Illustration des caractéristiques des 2 catégories de neurones de la corne dorsale de la moelle impliqués dans la transmission des messages nociceptifs :

B

neurone nociceptif spécifique



Enregistrement d'un neurone
Nociceptif spécifique



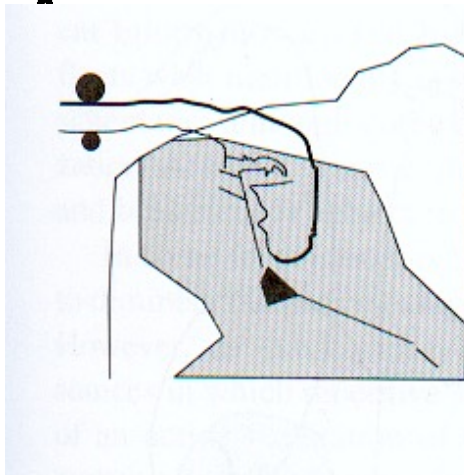
Brasseur (1997) fig.2-4a



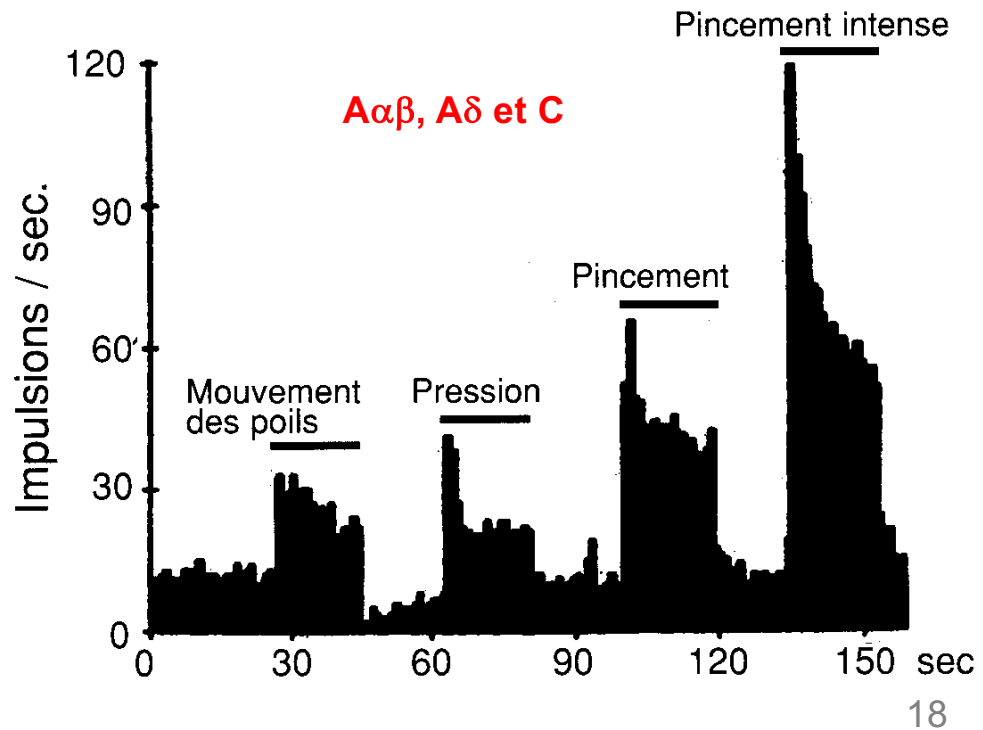
Neurones nociceptifs

Illustration des caractéristiques des 2 catégories de neurones de la corne dorsale de la moelle impliqués dans la transmission des messages nociceptifs :

neurone nociceptif non spécifique



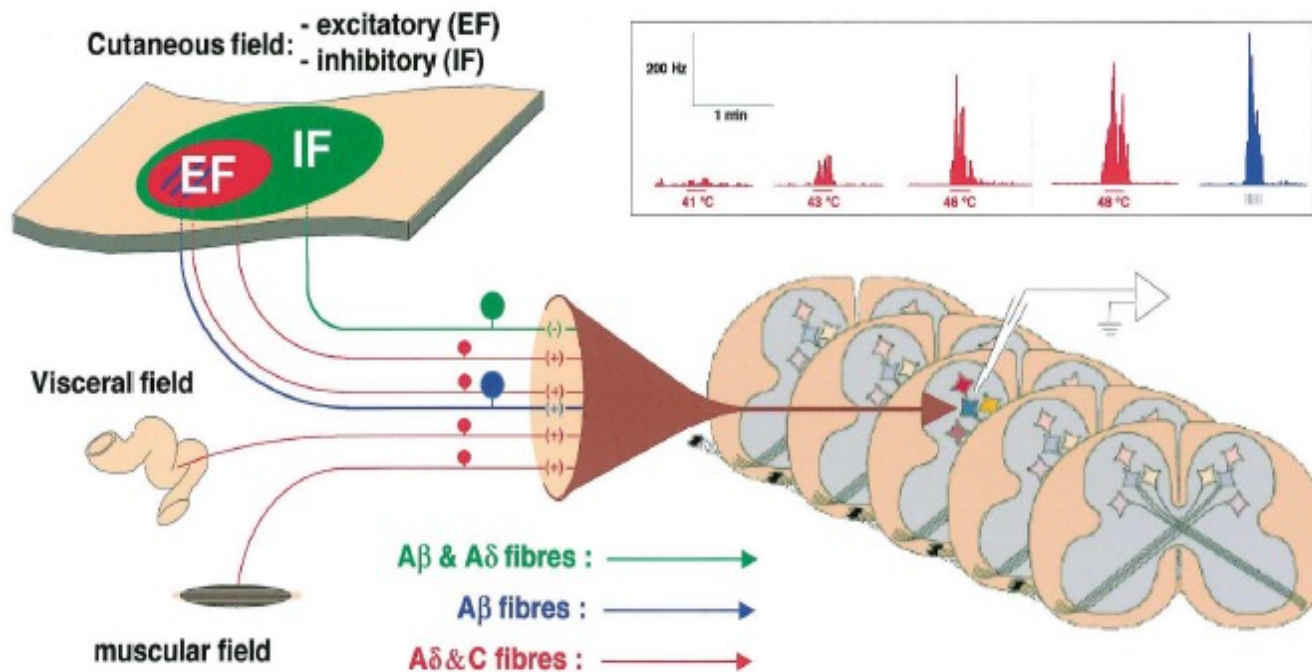
Enregistrement d'un neurone
Nociceptif non spécifique



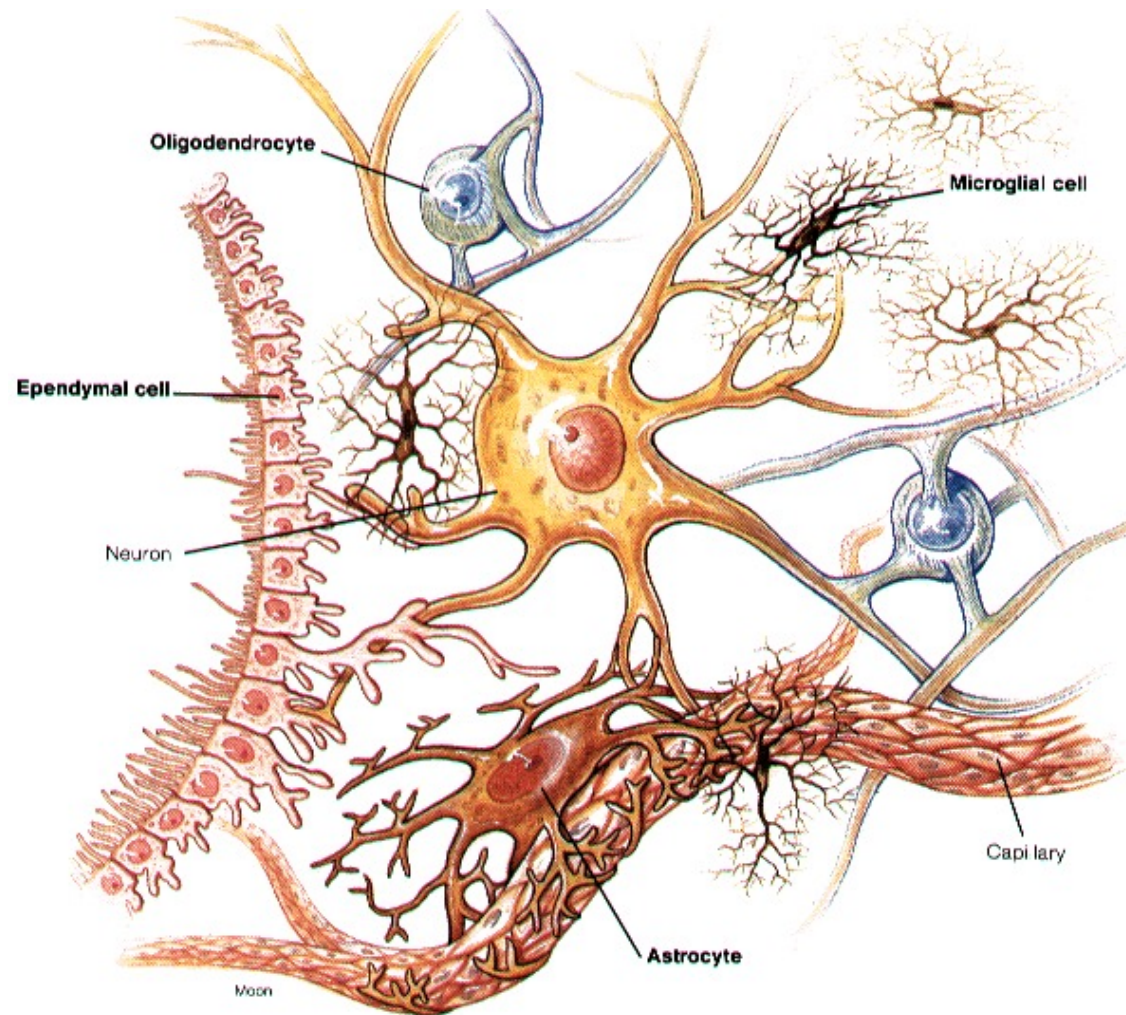
Brasseur (1997) fig.2-4a



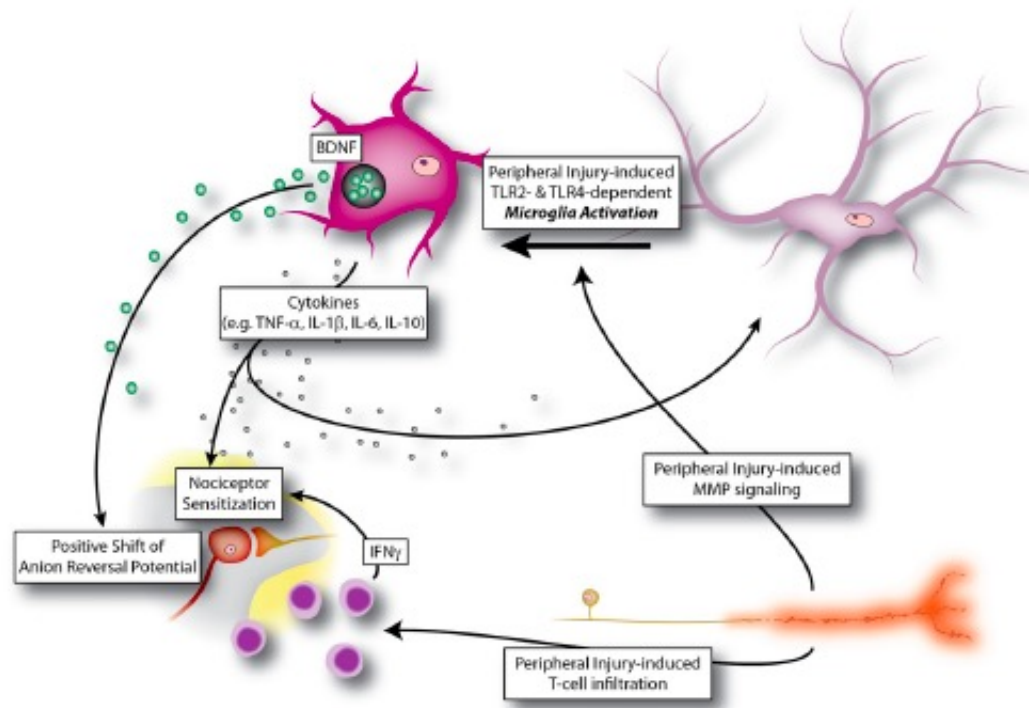
Convergences et réponses nociceptives



Cellules gliales



cellules gliales, système immunitaire et douleur



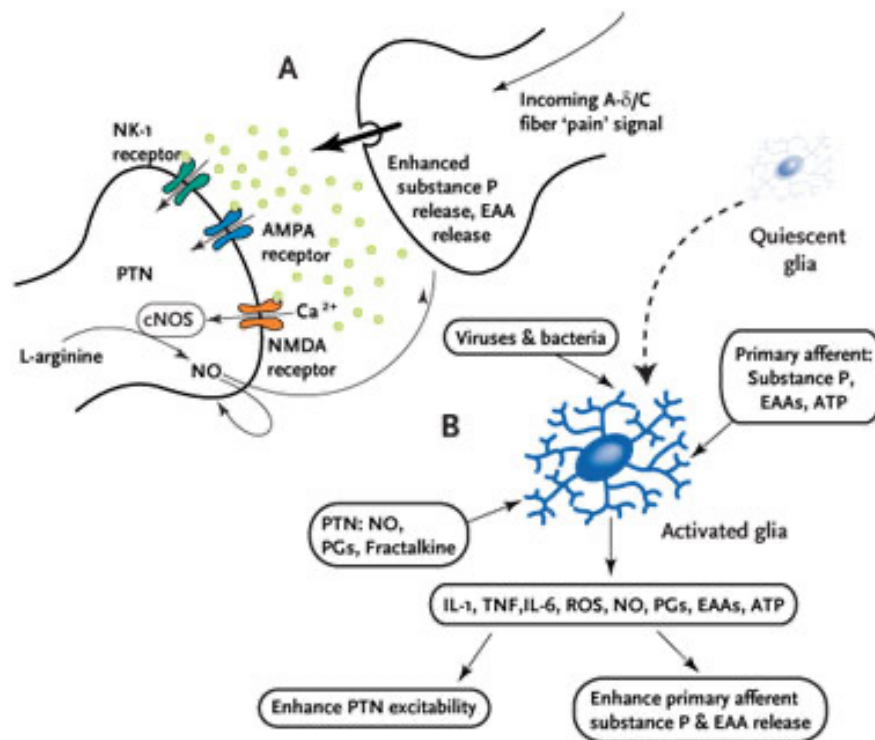
Christian A. von Hehn,^{1,2} Ralf Baron,³ and Clifford J. Woolf^{1,2,*} Neuron 73, February 23, 2012



Cellules gliales et douleur

L'activation de la microglie et des astrocytes provoque de l'hyperactivité cellulaire et le relâchement de substance P et d'AEE

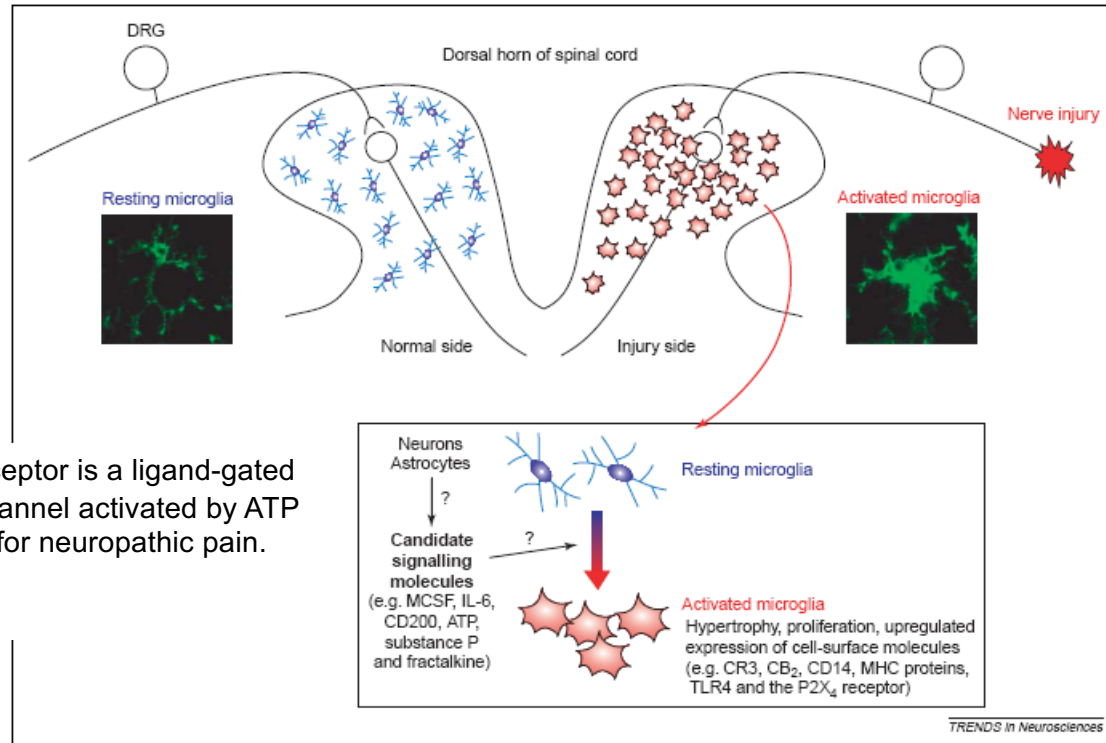
Il est important de tenir compte du rôle des cellules gliales qui sont activées par neurones nociceptifs



The Scientist, 28 Mars 2005: Watkins et al., *Trends Neurosci*, 24:450-5, 2001



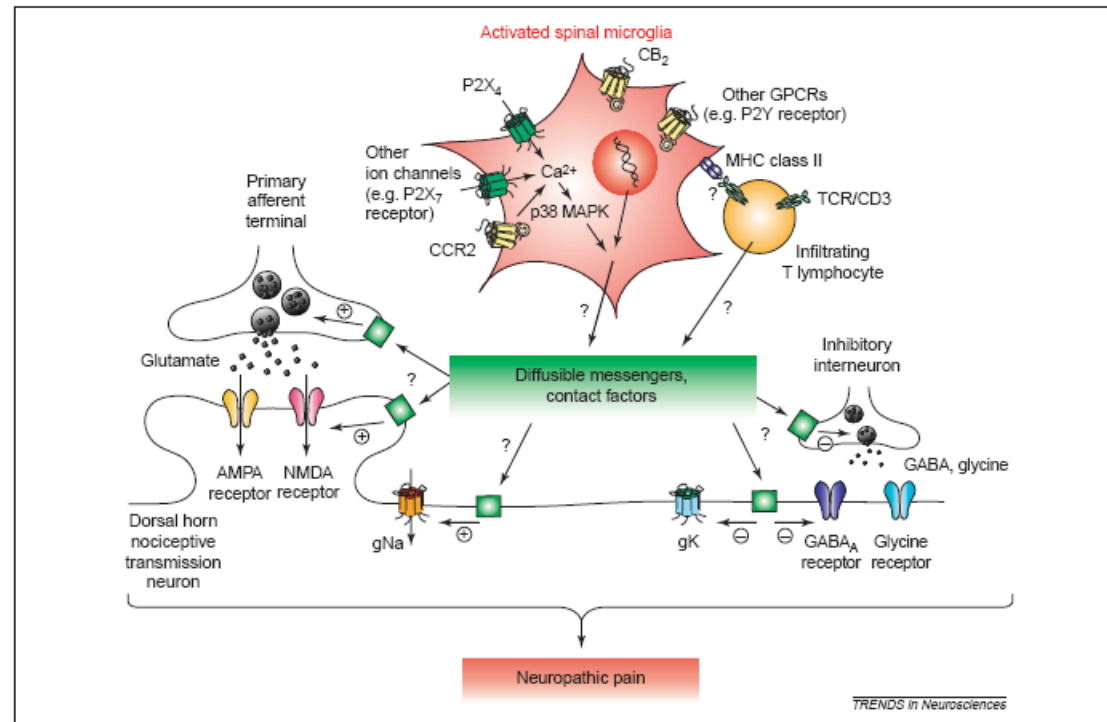
Makoto Tsuda^{1,2}, Kazuhide Inoue^{1,3} and Michael W. Salter²



P2X₄ receptor is a ligand-gated cation channel activated by ATP required for neuropathic pain.

Figure 1. Processes causing activation of microglia in the dorsal horn of the spinal cord following injury to a nerve in the periphery. On the normal side of dorsal horn, microglia have small somas, bearing thin and branched processes, and are homogeneously distributed (i.e. they are 'resting microglia'). After peripheral nerve injury, microglia in the spinal cord ipsilateral to the nerve injury transform from the resting to the 'activated microglia' phenotype, which is characterized by hypertrophy, proliferation and expression of cell-surface molecules (e.g. CR3, CB₂, CD14, MHC proteins, TLR4 and the P2X₄ receptor). Photographs show resting (left) and activated (right) microglia staining for CR3. Activation of microglia in the dorsal horn occurs predominantly in the central projection area of the injured peripheral nerve, which implies contribution of signals from injured nerve and/or affected dorsal horn neurons or astrocytes. Candidate signaling molecules include MCSF, IL-6, CD200, ATP, substance P and fractalkine.





The role of microglia in neuropathic pain:

- Release of glutamate
- Activation of the NMDA receptors
- Blocking of inhibition



Ma, J. Y. and Zhao, Z. Q.

The involvement of glia in long-term plasticity in the spinal dorsal horn of the rat.
Neuroreport 13 (14):1781-1784, 2002.

Stimulation tétanique = **LTP** fibres C spinales

Stimulation tétanique avec fluorocitrate (inh
activité gliale) = **LTD** fibres C spinales

Cellules gliales et LTP

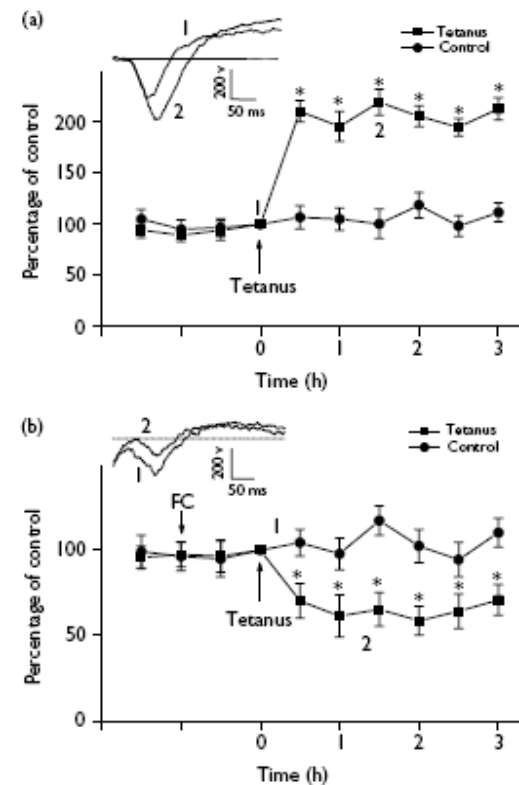
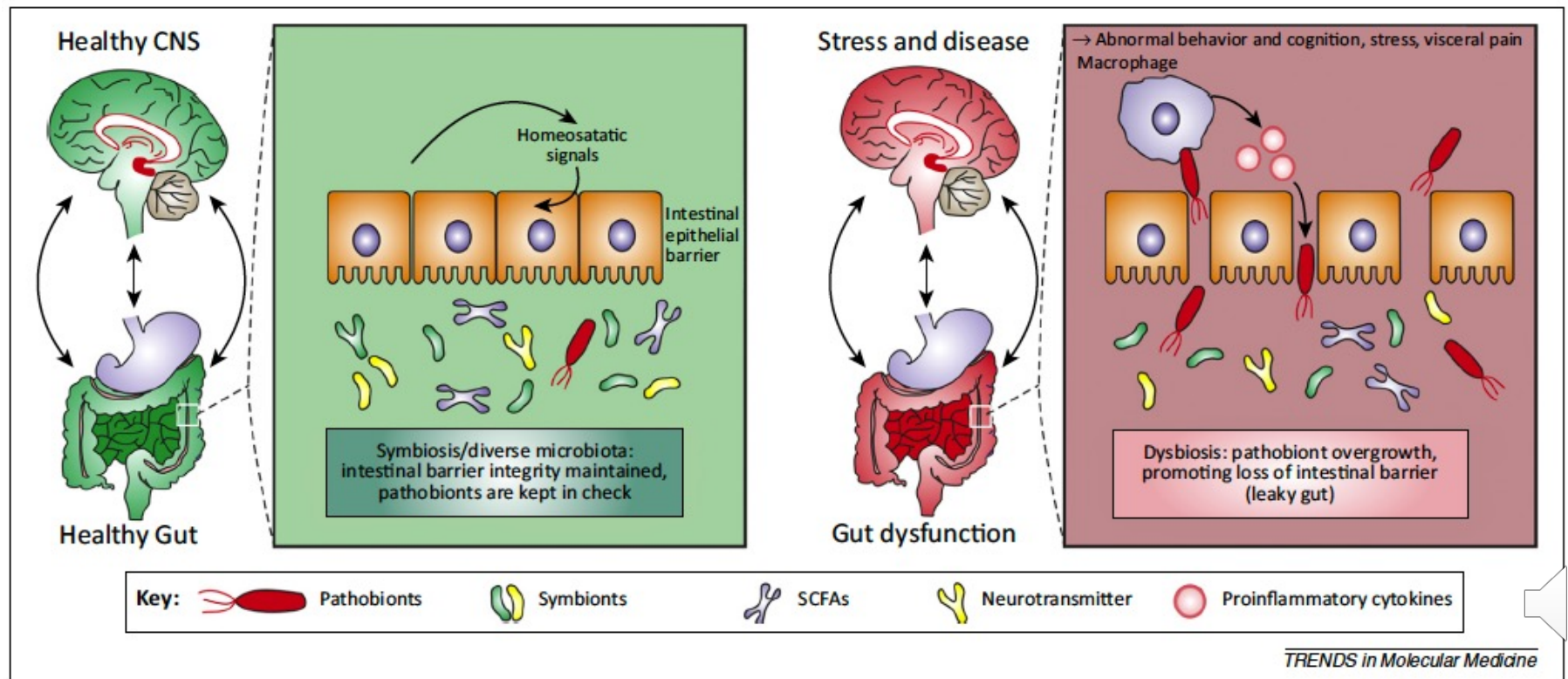


Fig. 1. LTD is induced with prior fluorocitrate administration. Tetanic stimulation induces LTP of C fiber evoked field potentials are shown in (a). (b) Tetanic stimulation produces LTD when fluorocitrate (1 nmol) is given 1 h before. Mean amplitude ($\pm$ s.e.m.) was expressed as percentage of control and was plotted vs time. * $p < 0.05$ vs control. Insets illustrate the original C fibers evoked field potentials before and after tetanus. Bars = 200 μ V, 50 ms.



Microbiota and neurodevelopmental windows: implications for brain disorders

Yuliya E. Borre¹, Gerard W. O'Keefe^{2,3}, Gerard Clarke^{1,4}, Catherine Stanton^{4,5}, Timothy G. Dinan^{1,4}, and John F. Cryan^{1,2}



The effects of gut microbiota on CNS function in humans

Kirsten Tillisch

- Role for the microbiota in broad aspects of human health, including mood, cognition, and chronic pain.
- Altering the microbiota with beneficial bacteria, or probiotics, can lead to changes in brain function, as well as subjective reports of mood.
- Bidirectional communication between the brain and microbiota ... provide novel methods to enhance health and treat disease.

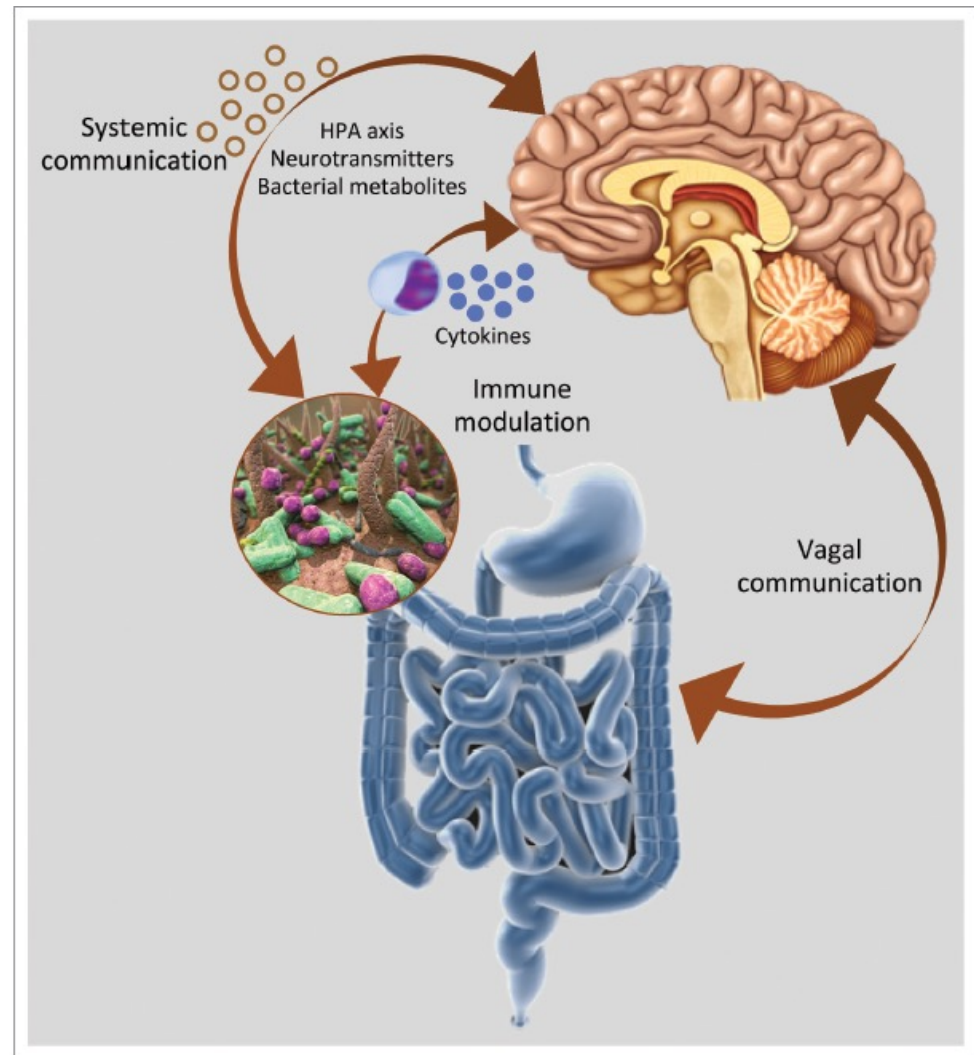
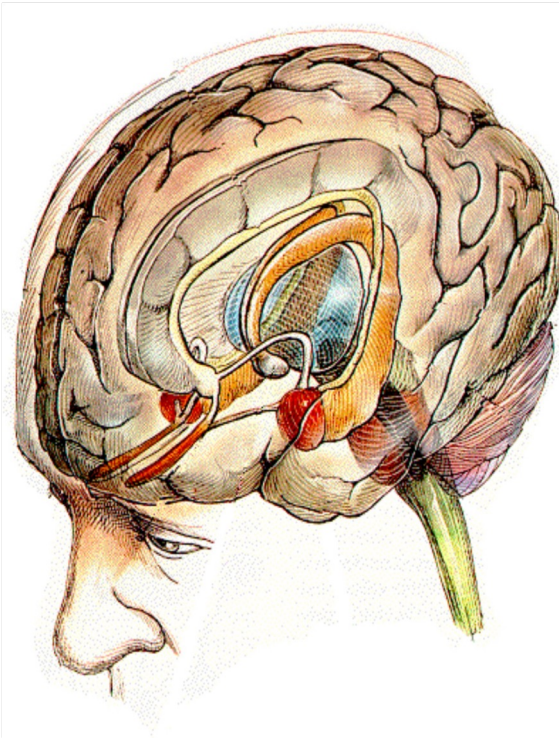


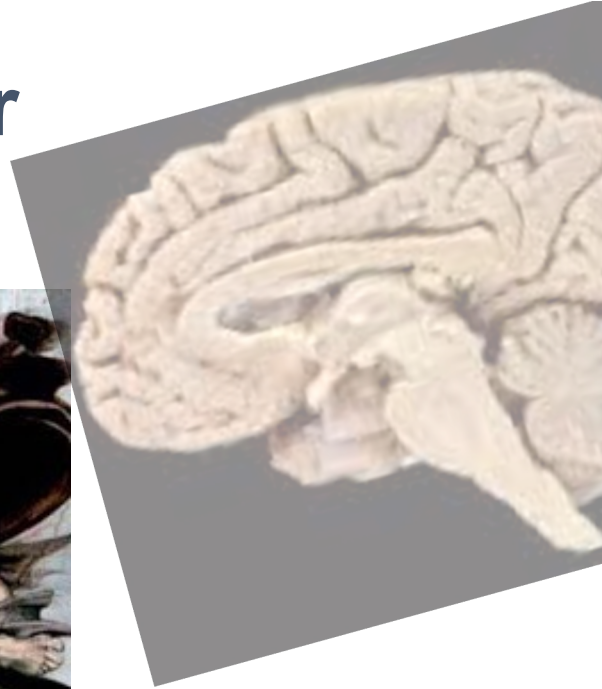
Figure 1. Potential routes of communication between the microbiota and the brain are shown. Multiple inputs from the periphery can act centrally to modulate mood, pain sensitivity, cognition, and behavior.



Centres supérieurs et douleur



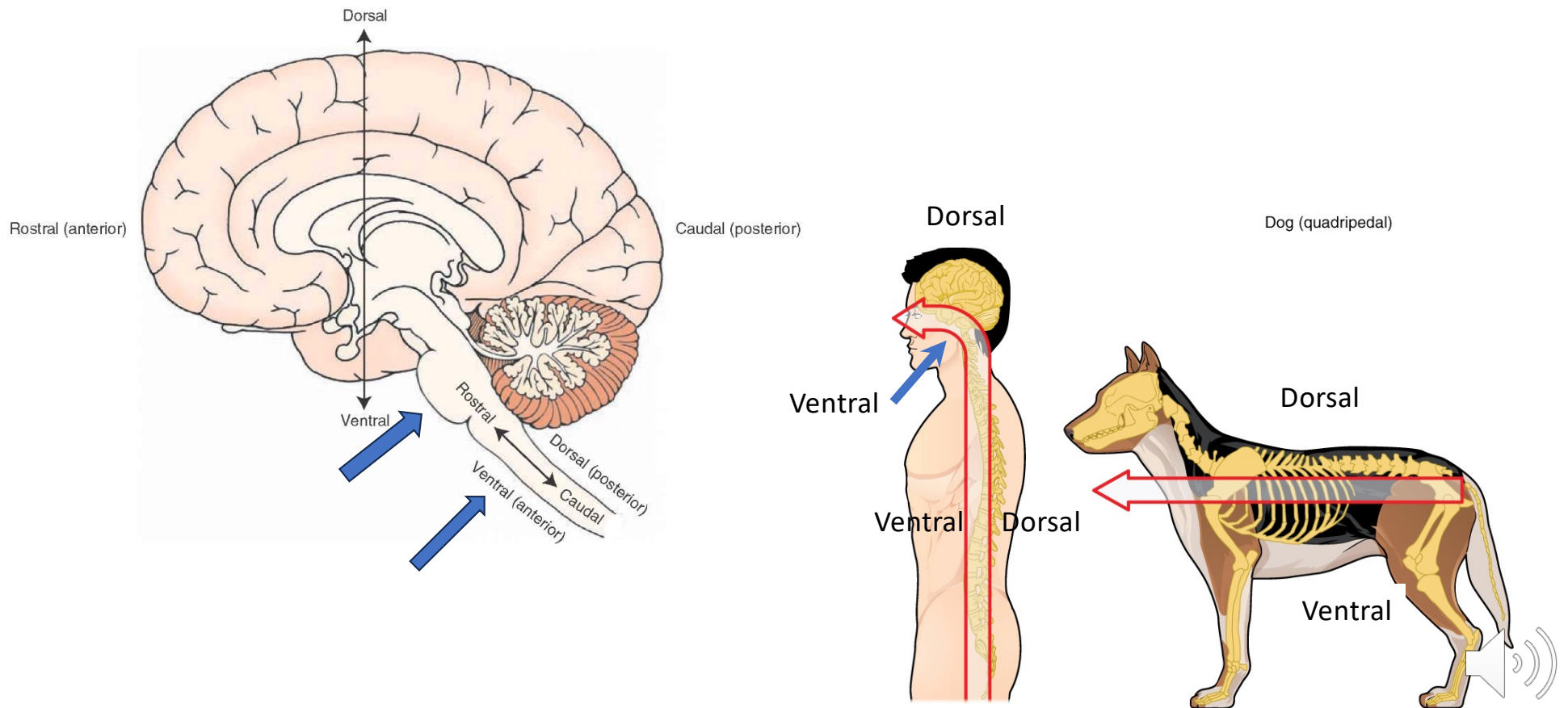
Centres supérieurs et douleur



Meshberger, F. "An interpretation of Michelangelo's Creation of Adam Based on Neuroanatomy" (JAMA 264:1837-1841, 1990)

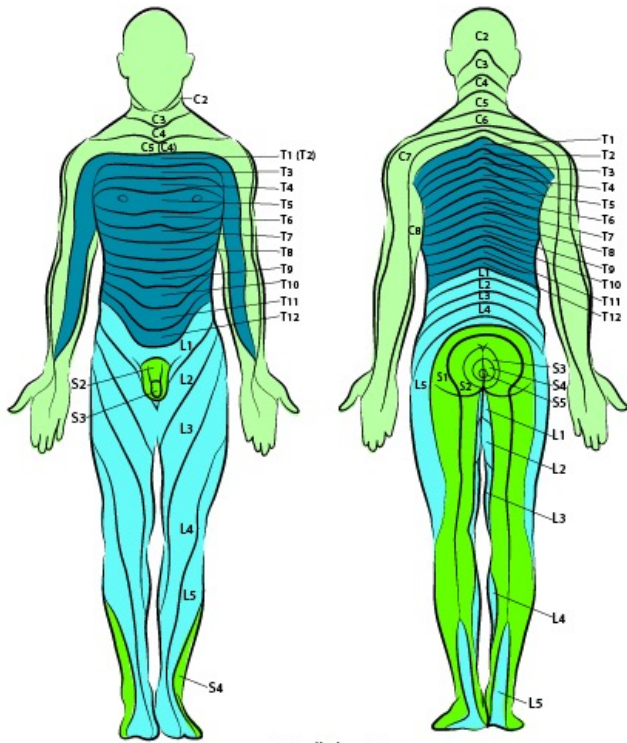


Orientation du système nerveux central

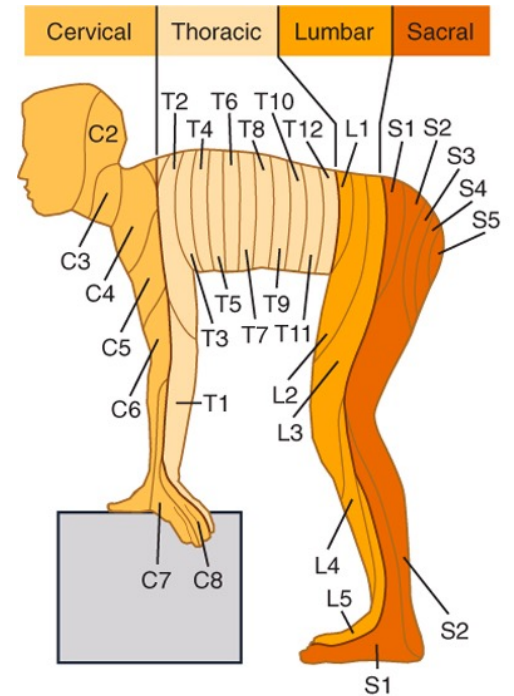
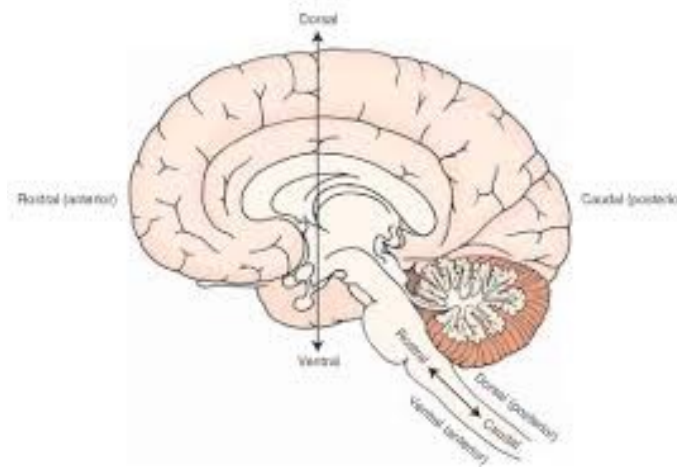


Orientation du système nerveux central

Dermatomes (Map and Locations on Skin)



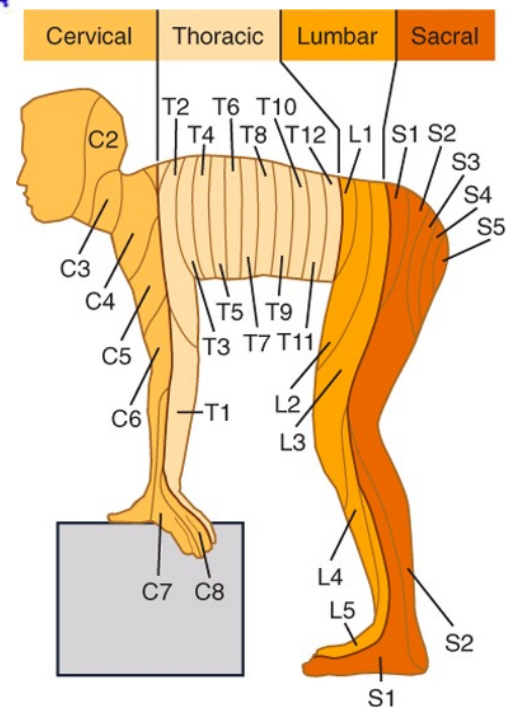
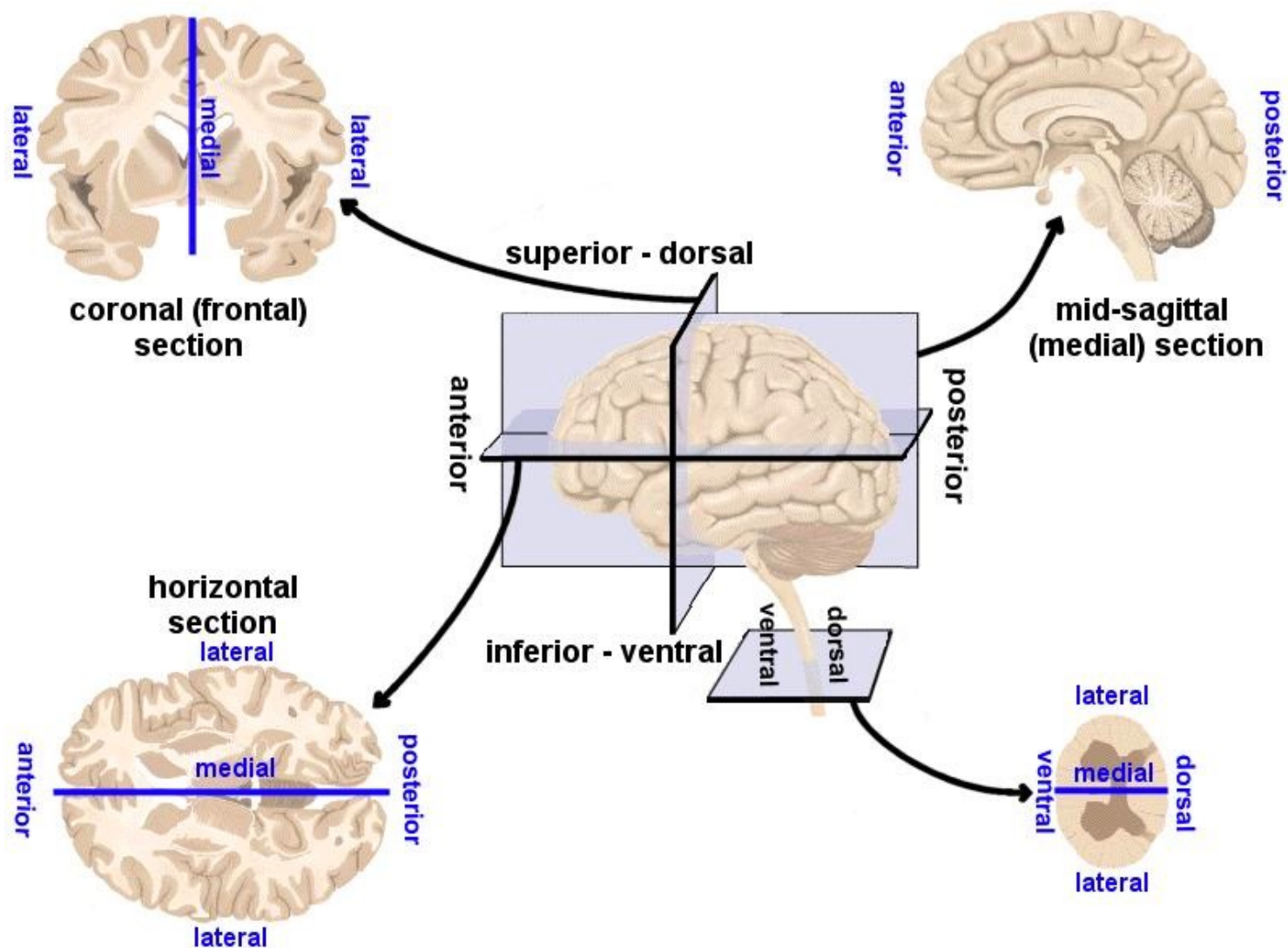
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Koeppen & Stanton: Berne and Levy Physic
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Koeppen & Stanton: Berne and Levy Physic
Copyright © 2008 by Mosby, an imprint of



<http://kleacrymeariver.weebly.com/planes-of-orientation.html>

Si le cerveau n'était pas replié, il ferait environ 1 m²

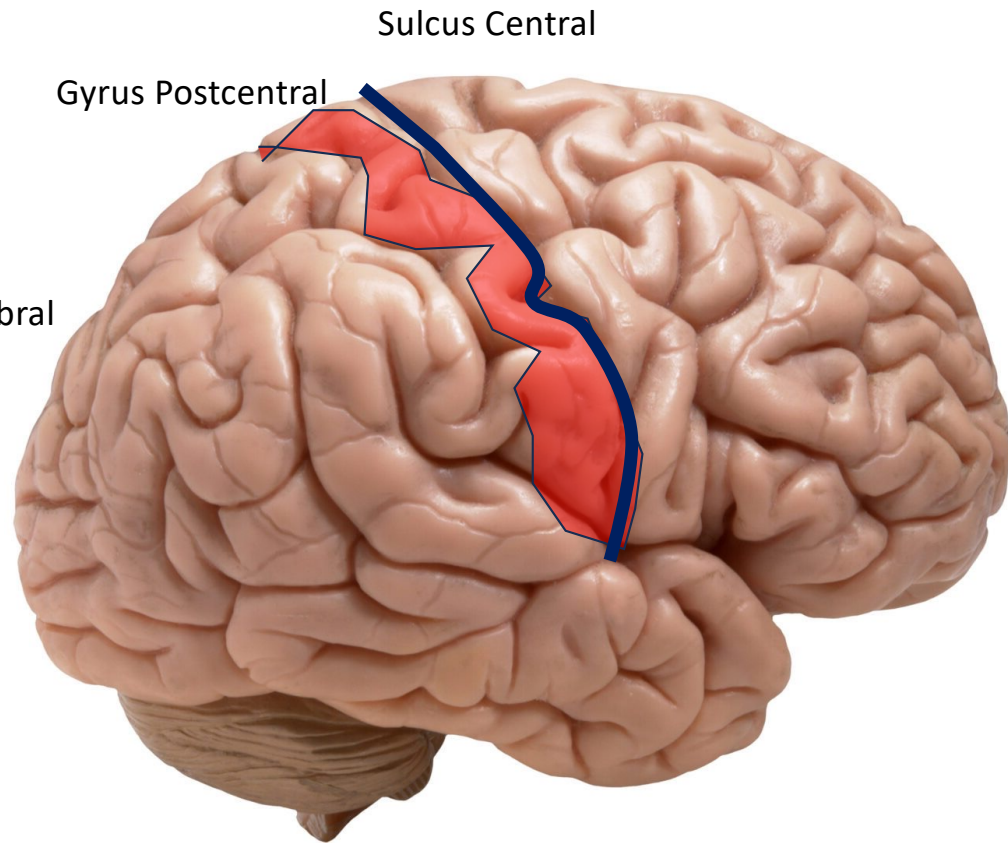


Sulcus:

Dépression ou sillon dans le cortex cérébral.

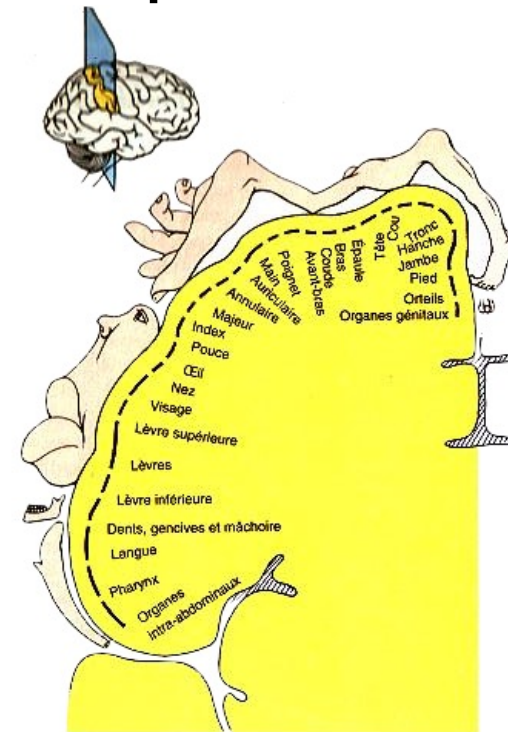
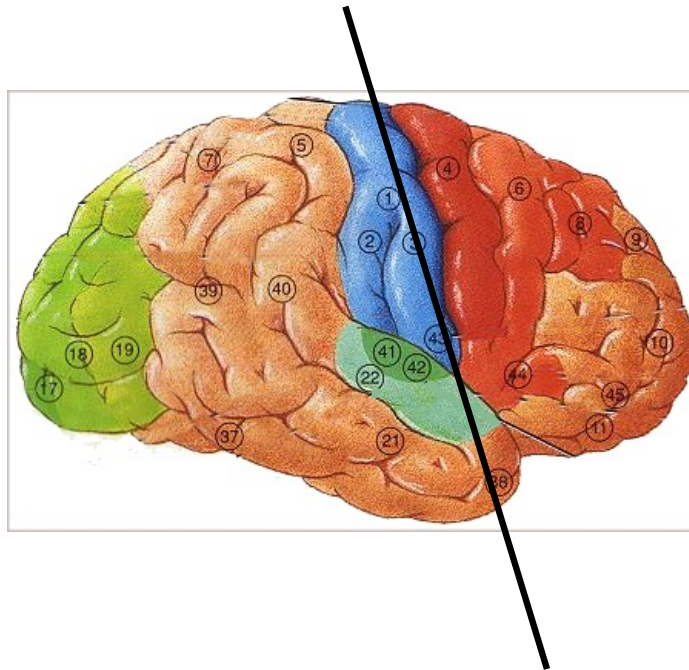
Gyrus

Circovolution ou renflement sur le cortex cérébral



Homuncules de Penfield

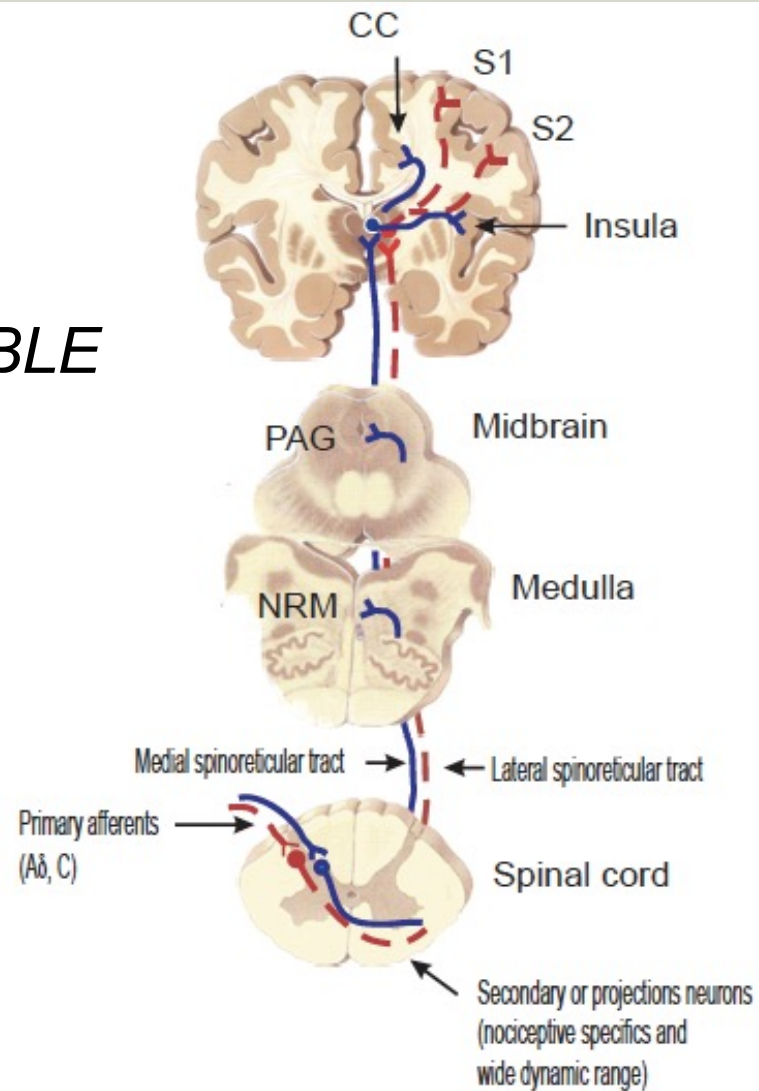
Cortex somatosensoriel primaire



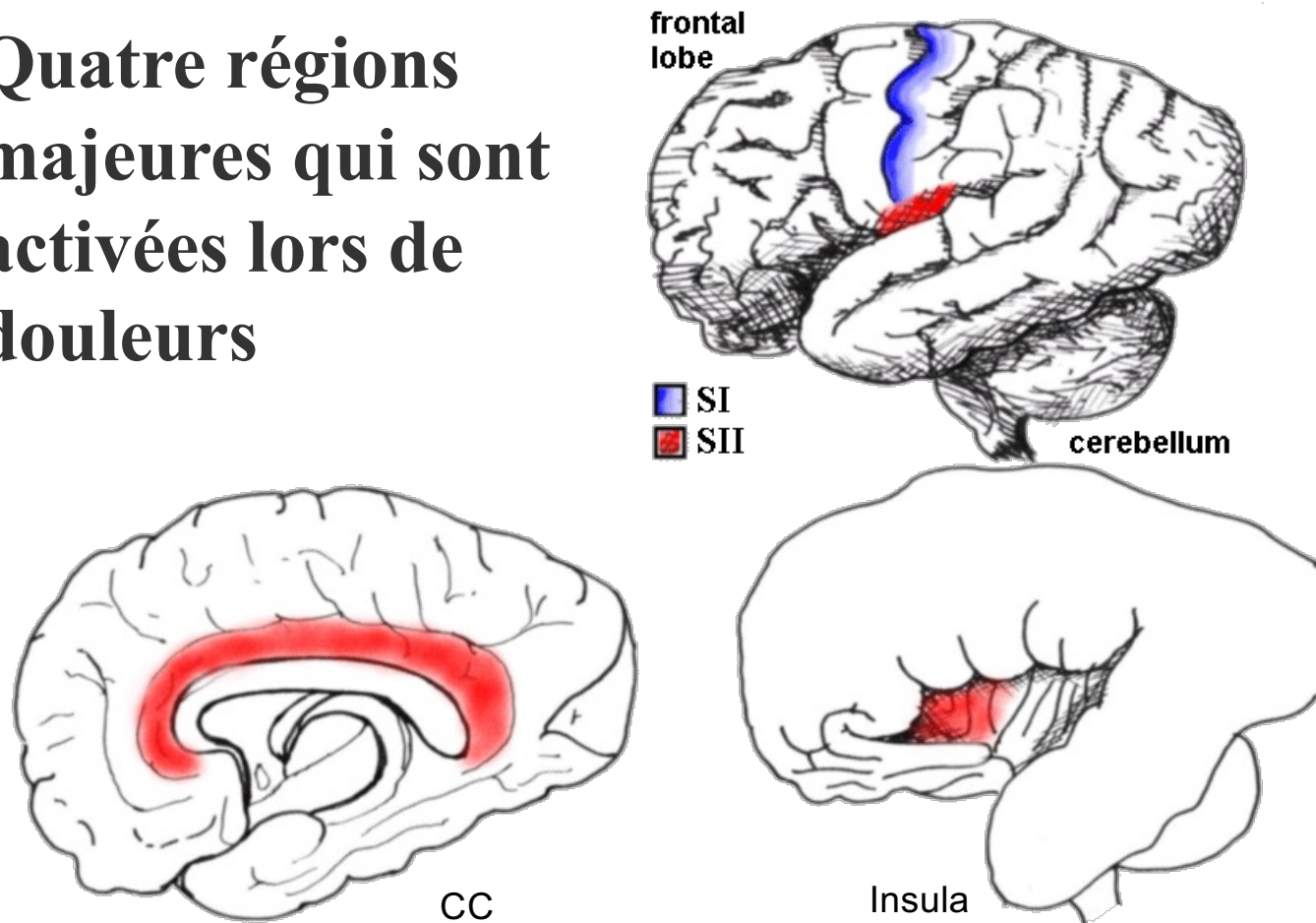
a) Cortex somesthésique de l'hémisphère cérébral droit



*INTENSITÉ
ET
ASPECT DÉSAGRÉABLE*



Quatre régions majeures qui sont activées lors de douleurs



Système limbique

Cortex cingulaire

Thalamus

Hypothalamus

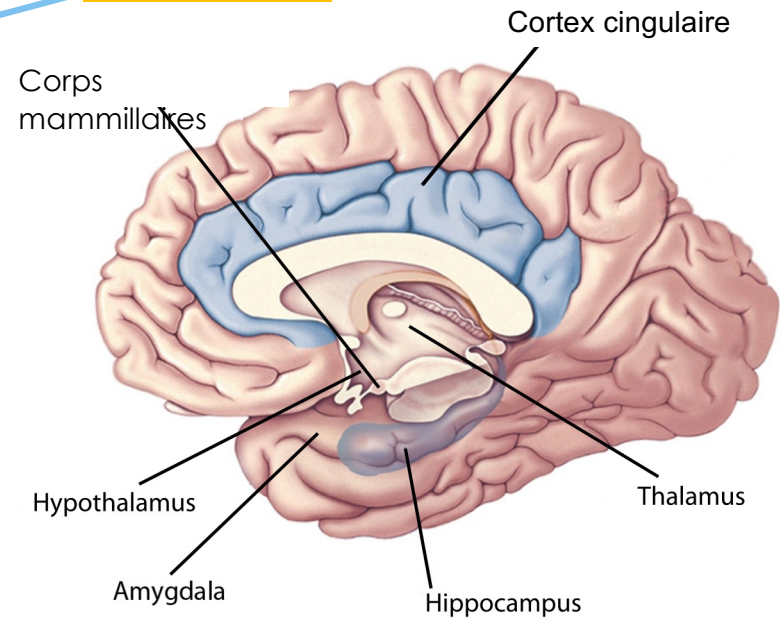
Hippocampe

Corps mammillaires

Amygdale

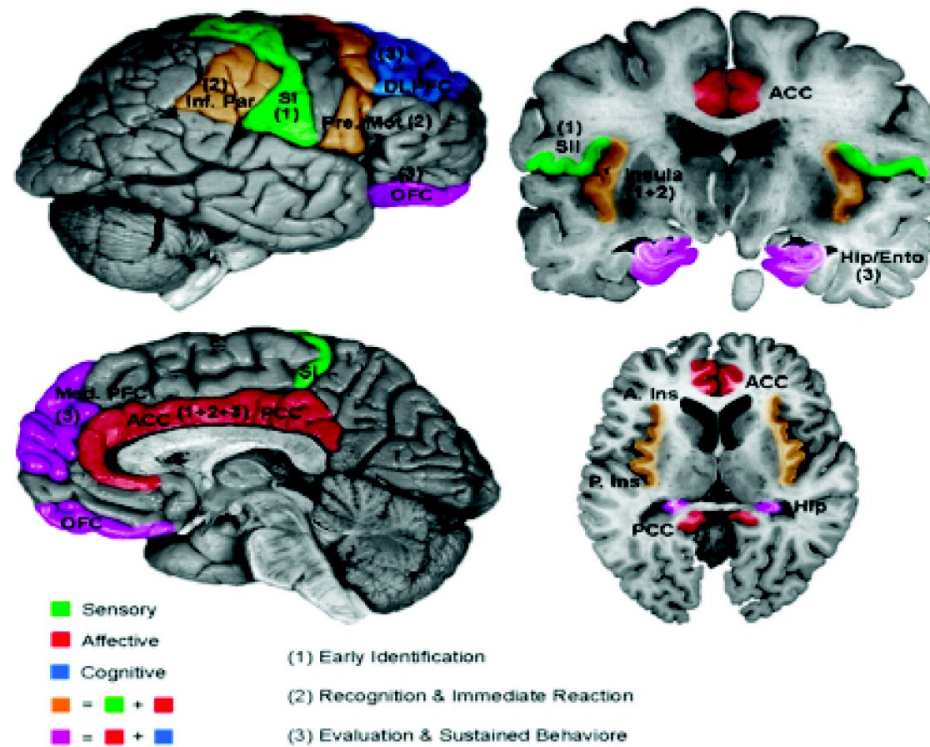
Attentes
Émotions
Anxiété

...

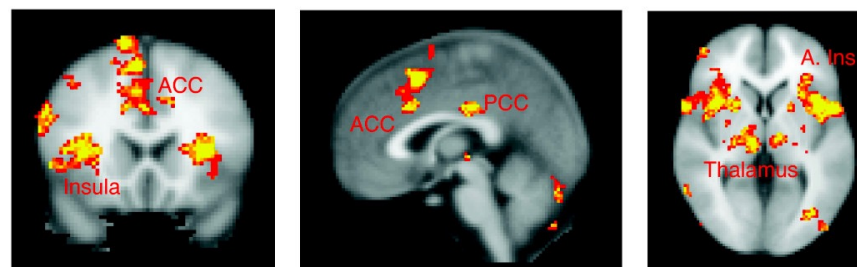


Functional measures

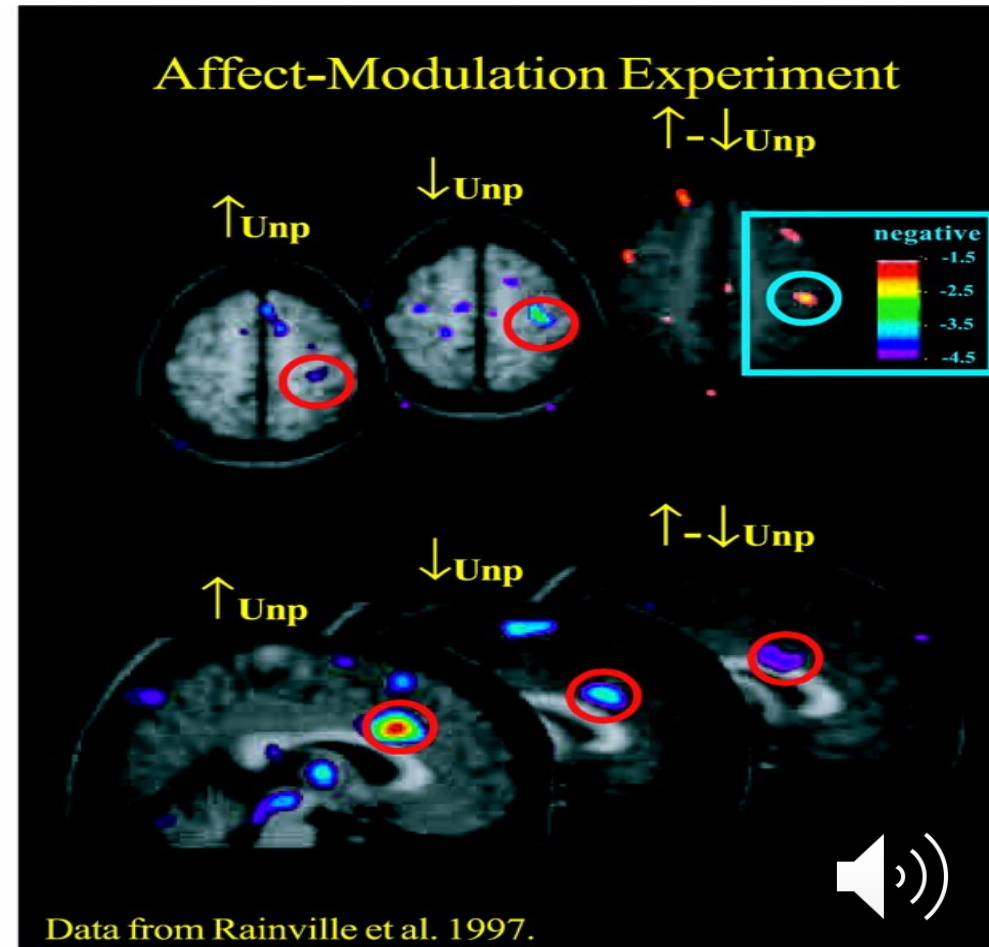
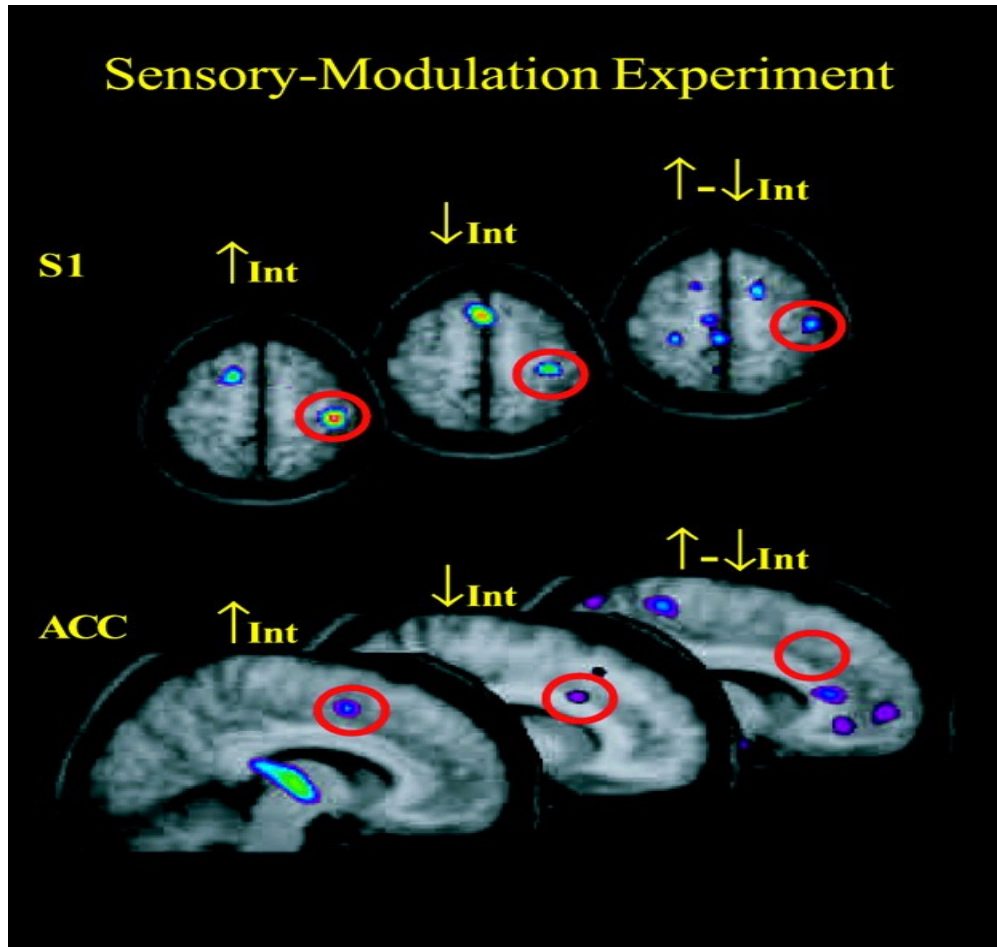
A. Brain areas functionally related to pain processing.



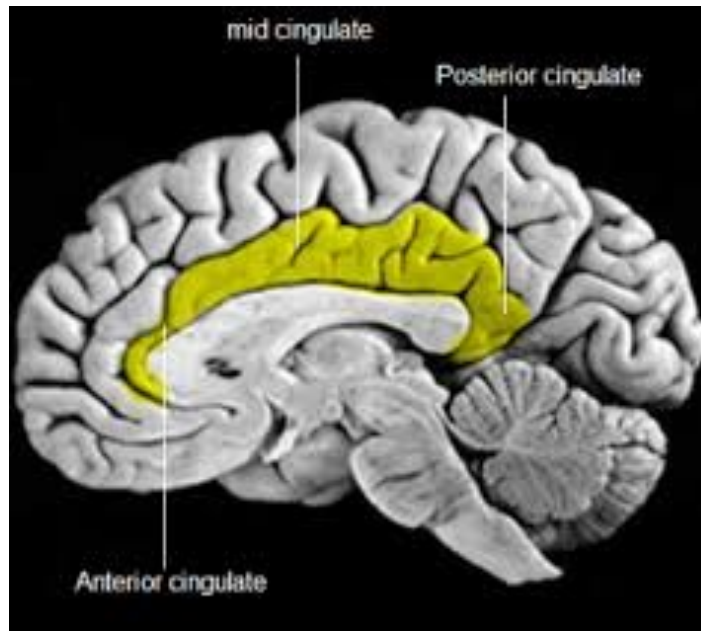
B. Example of functional MRI response to painful stimulation.



Manipulations indépendantes des composantes sensorielles et affectives de la douleur



Cortex cingulé



CCA: Émotions et douleur
CCA: Peur et douleur
CCP: Salience



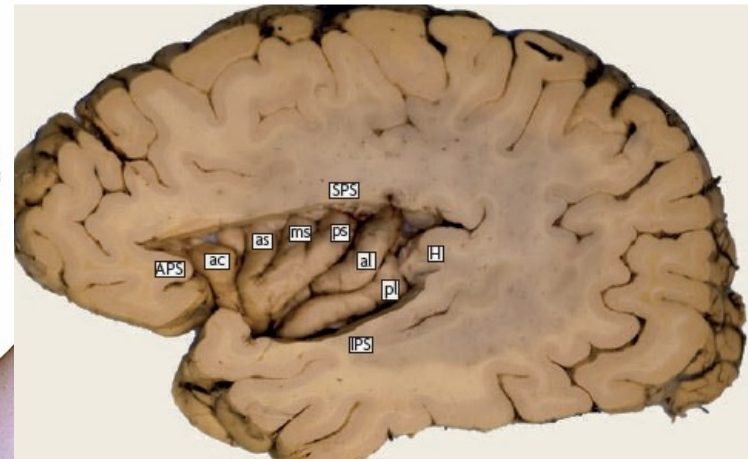
OPINION

How do you feel — now? The anterior insula and human awareness

A. D. (Bud) Craig



Copyright © 2002 by Mosby, Inc.



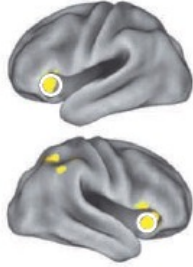
Error awareness



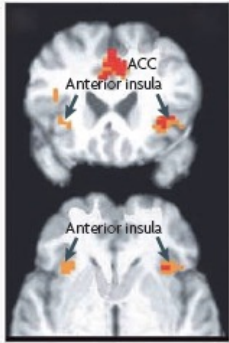
'Free won't'



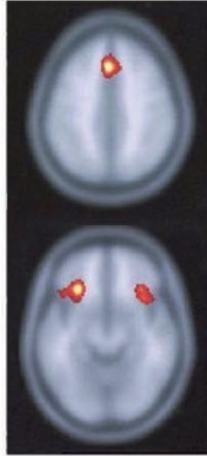
Moment of recognition



Decision making



'Feeling of knowing'



Inspection time



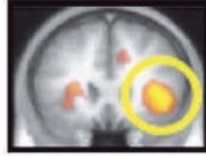
Time perception



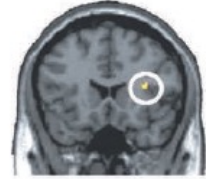
Subjective cooling



Attention to heat pain



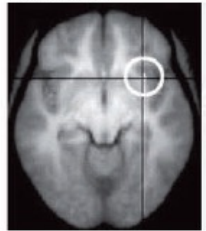
Heartbeat awareness



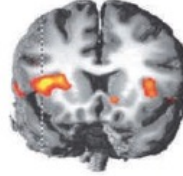
Learned pain 'now'



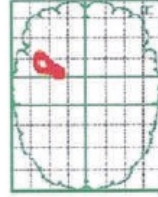
Self recognition



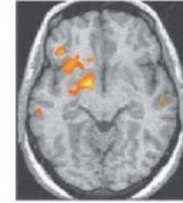
Pleasant music



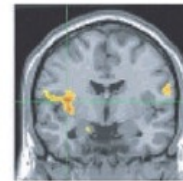
Rhythm



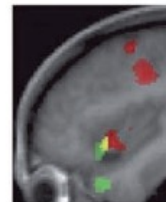
Maternal affiliation



Happy voices



Seeing or making a smile



OPINION

How do you feel — now? The anterior insula and human awareness

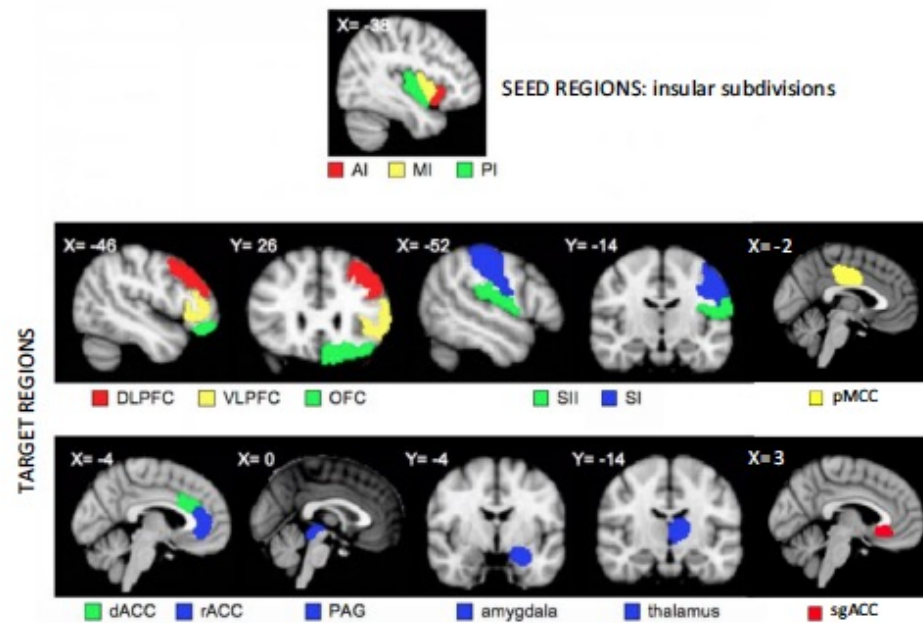
A. D. (Bud) Craig



Differential structural and resting state connectivity between insular subdivisions and other pain-related brain regions



K. Wiech^{a,b,*}, S. Jabdi^a, C.S. Lin^{a,b}, J. Andersson^a, I. Tracey^{a,b}

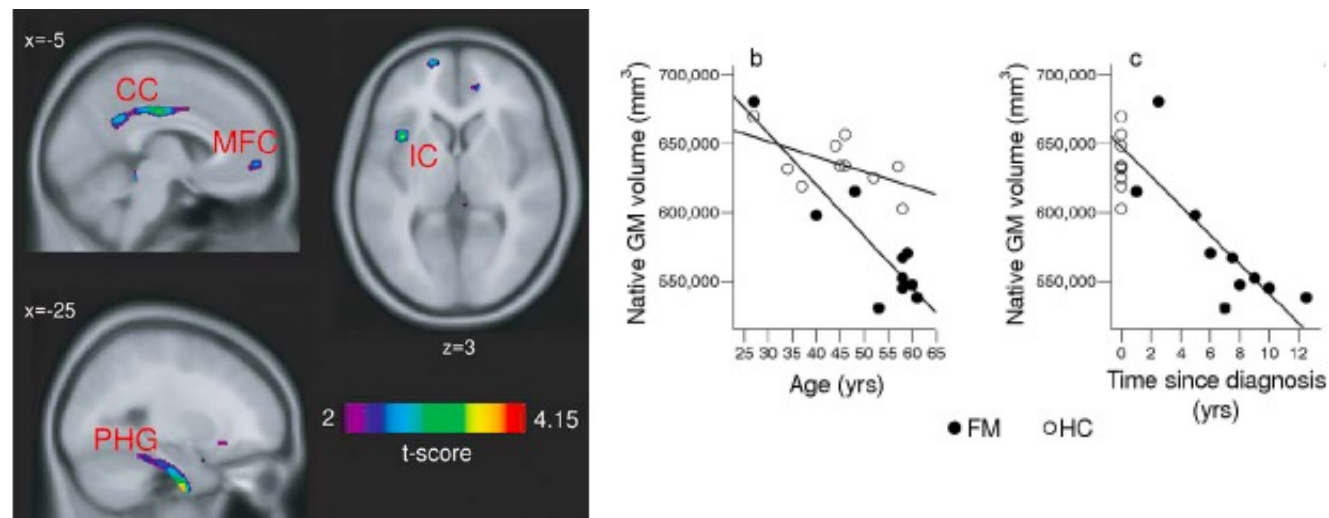


Effet de la douleur sur le cerveau



Accelerated Brain Gray Matter Loss in Fibromyalgia Patients: Premature Aging of the Brain?

Anil Kuchinad,^{1,2} Petra Schweinhardt,¹ David A. Seminowicz,¹ Patrick B. Wood,¹ Boris A. Chizh,⁴ and M. Catherine Bushnell^{1,2,3}

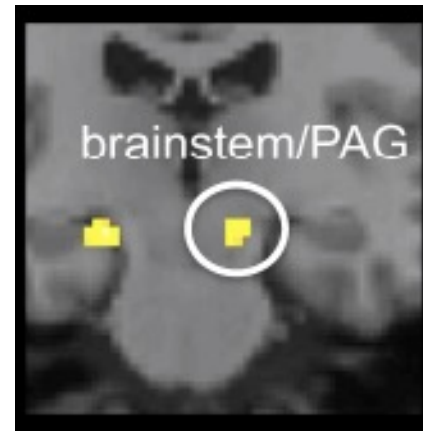
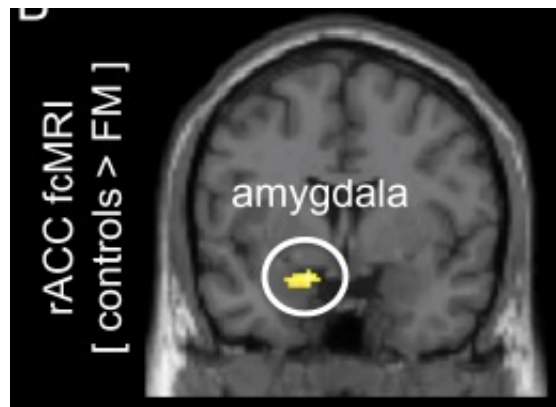


The Journal of Neuroscience, April 11, 2007 • 27(15):4004–4007



Patients With Fibromyalgia Display Less Functional Connectivity In The Brain's Pain Inhibitory Network

Molecular Pain 2012, 8:32 doi:10.1186/1744-8069-8-32



Patients with FM displayed less connectivity within the brain's pain inhibitory network during calibrated pressure pain, compared to healthy controls.

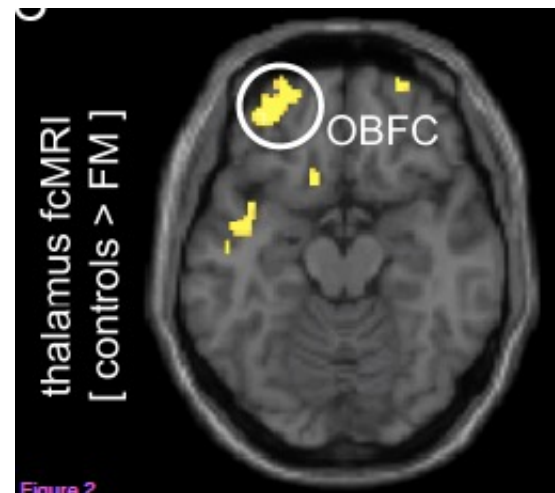


Figure 2





Pain 137 (2008) 7–15

PAIN

www.elsevier.com/locate/pain

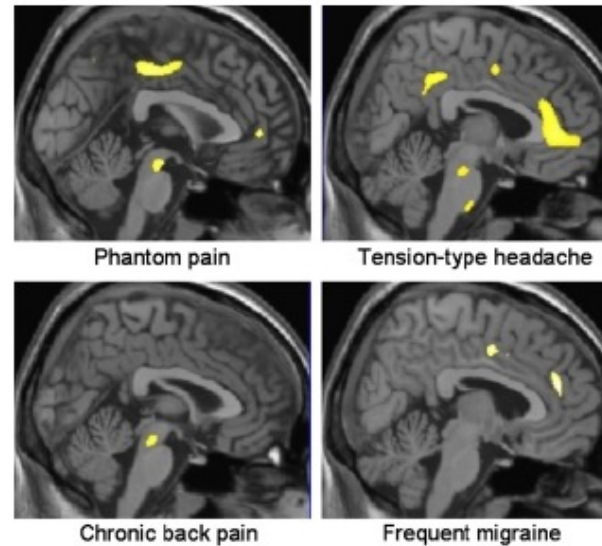
Review

Chronic pain may change the structure of the brain

Arne May*

Statistical parametric maps demonstrating the structural difference in gray matter between chronic pain patients and unaffected control subjects. Significant gray matter decrease is shown for each single group of patients, compared to match healthy controls and is superimposed in yellow color on a normalized image of a healthy control subject.

Pas uniquement pour les patients qui souffrent de fibromyalgie !

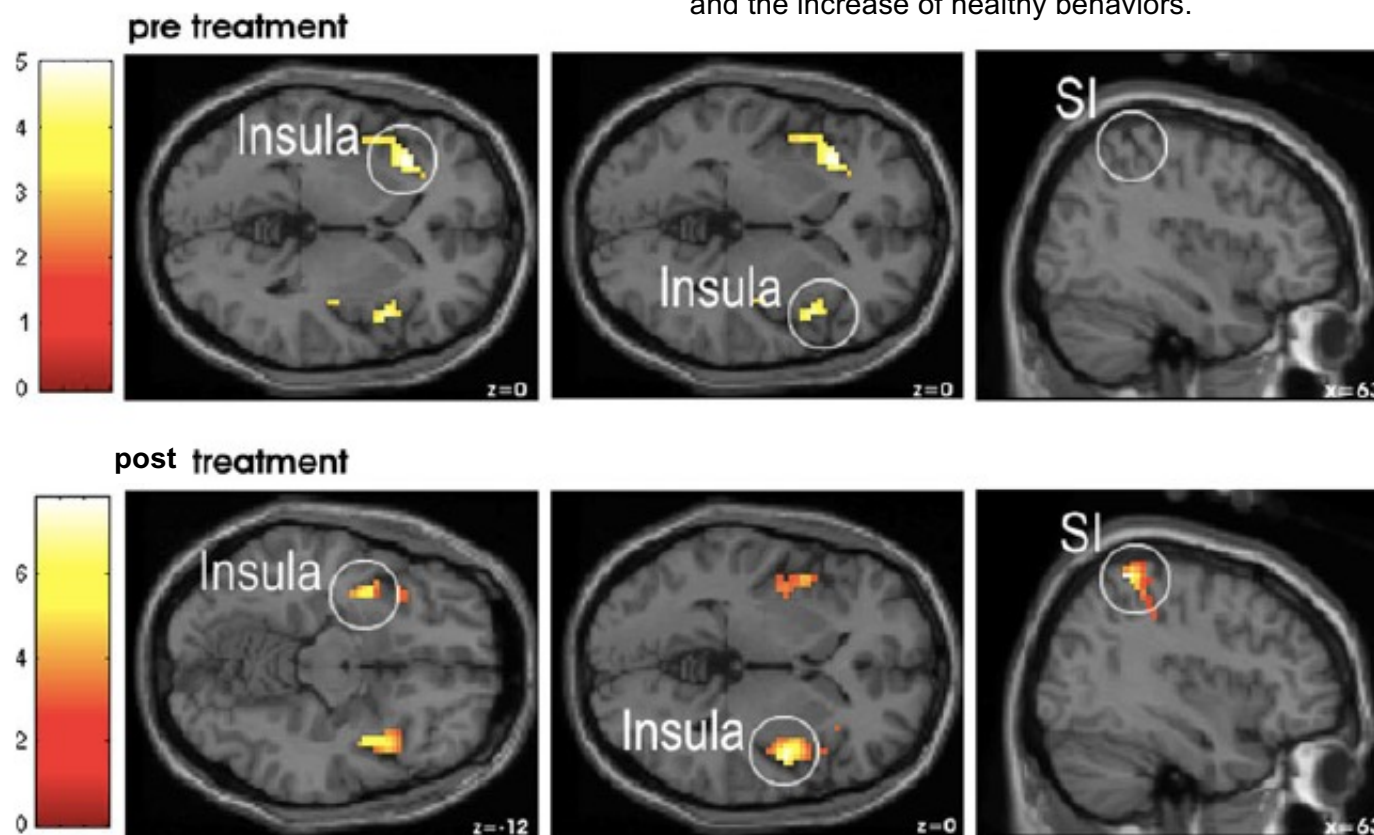


Treatment-related changes in brain activation in patients with fibromyalgia syndrome

Martin Diers · Pinar Yilmaz · Mariela Rance · Kati Thieme ·
Richard H. Gracely · Claudia Rolko · Marcus T. Schley ·
Ulrike Kiessling · Haili Wang · Herta Flor

Exp Brain Res (2012) 218:619–628

The treatment consisted of 12 weekly 2-h sessions led and focused on the extinction of pain-related behaviors and the increase of healthy behaviors.



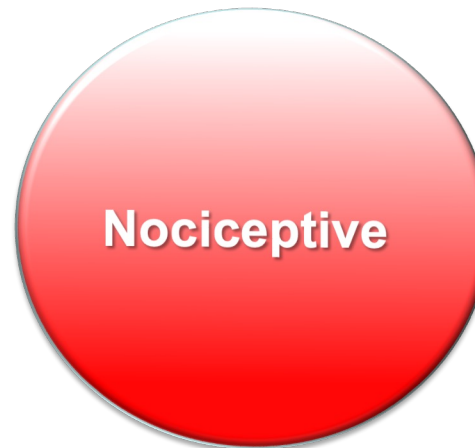
Douleur



Le patient a mal, mais il souffre de quoi?

Nociceptive

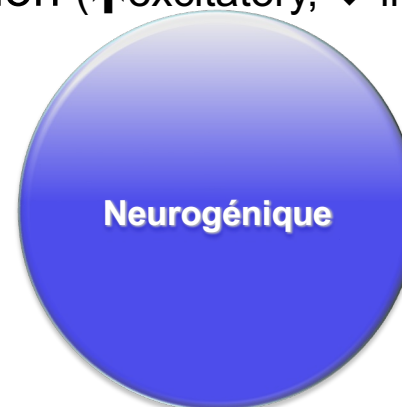
- Réponse à la suite d'une stimulation potentiellement dangereuse pour l'organisme (mécanique, chimique, thermique)
- Lacération, fracture, ischémie...



Le patient a mal, mais il souffre de quoi?

Neurogénique

- Douleur à la suite d'une lésion ou une dysfonction du SNC
- Lésion nerf, neuropathies, sensibilisation centrale...
- Sensibilisation centrale : Dysfonction des mécanismes endogènes de modulation (↑ excitatory, ↓ inhibitory)



Nociceptive ou neurogénique?

Nociceptive

Neurogénique



Conclusion

- De la périphérie aux centres supérieurs, le signal nociceptif est modulé avant de devenir une douleur.
- Même pour les douleurs chroniques centralisées, il est important de vérifier si une composante nociceptive participe au maintien de la douleur.

