X Programa de Educação Continuada em Fisiopatologia e Terapêutica da Dor – 2020

Equipe de Controle de Dor da Divisão de Anestesia do Instituto Central do Hospital das Clínicas da FMUSP

Neuroimagem, placebo e dor.

Fábio Porto, neurologista cognitivo e do comportamento
Instituto de Psiquiatria- IPQ- HCFMUSP

"Dor é uma experiência sensitiva e emocional desagradável associada com danos reais ou potenciais em tecidos, ou assim percepcionada como dano.

Fenômeno subjetivo

International Association for the Study of Pain

Lessons from Anti-Amyloid-β Immunotherapies in Alzheimer Disease: Aiming at a Moving Target

with consistent clinical benefits. ***Conclusions:*** Despite the overall disappointing results, there is still hope that Aβ immunotherapy in presymptomatic patients will prevent neuronal loss and provide significant clinical benefits that can be applied to larger populations as preventive therapies. Advances with other targets may soon provide additional therapeutic options for AD with increased efficacy.

Cwang., et al, 2017 Neurodegener Dis 2017

The National Institute of Mental Health: https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml

The National Institute of Mental Health: www.nimh.nih.gov

Research Domain Criteria (RDoC)

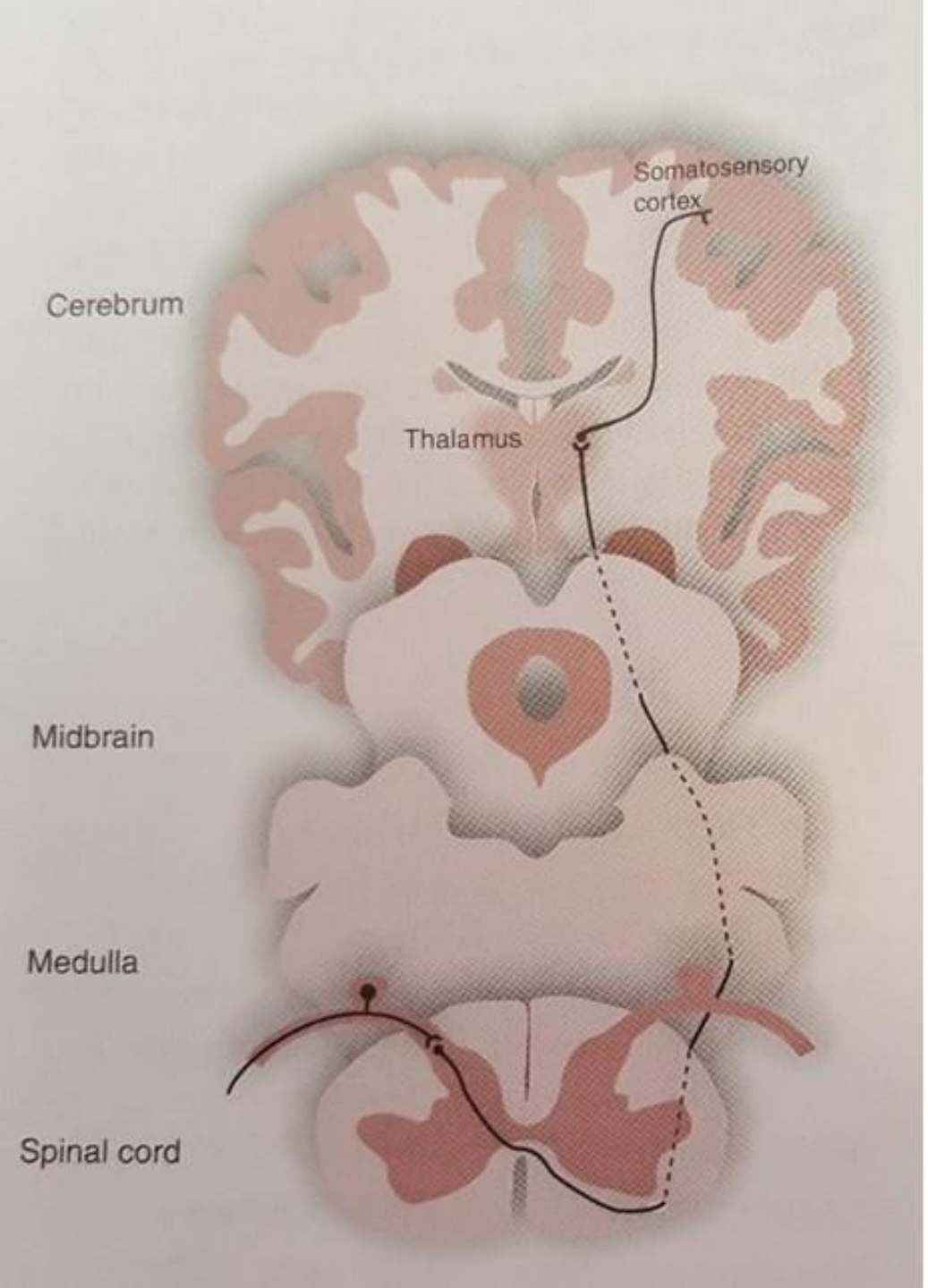
RDoC is a research framework for new approaches to investigating mental disorders. It integrates many levels of information (from genomics and circuits to behavior and self-reports) in order to explore basic dimensions of functioning that span the full range of human behavior from normal to abnormal. RDoC is not meant to serve as a diagnostic guide, nor is it intended to replace current diagnostic systems. The goal is to understand the nature of mental health and illness in terms of varying degrees of dysfunctions in general psychological/biological systems.

Subscribe for RDoC announcements, funding opportunities, and events

Join the RDoC Discussion

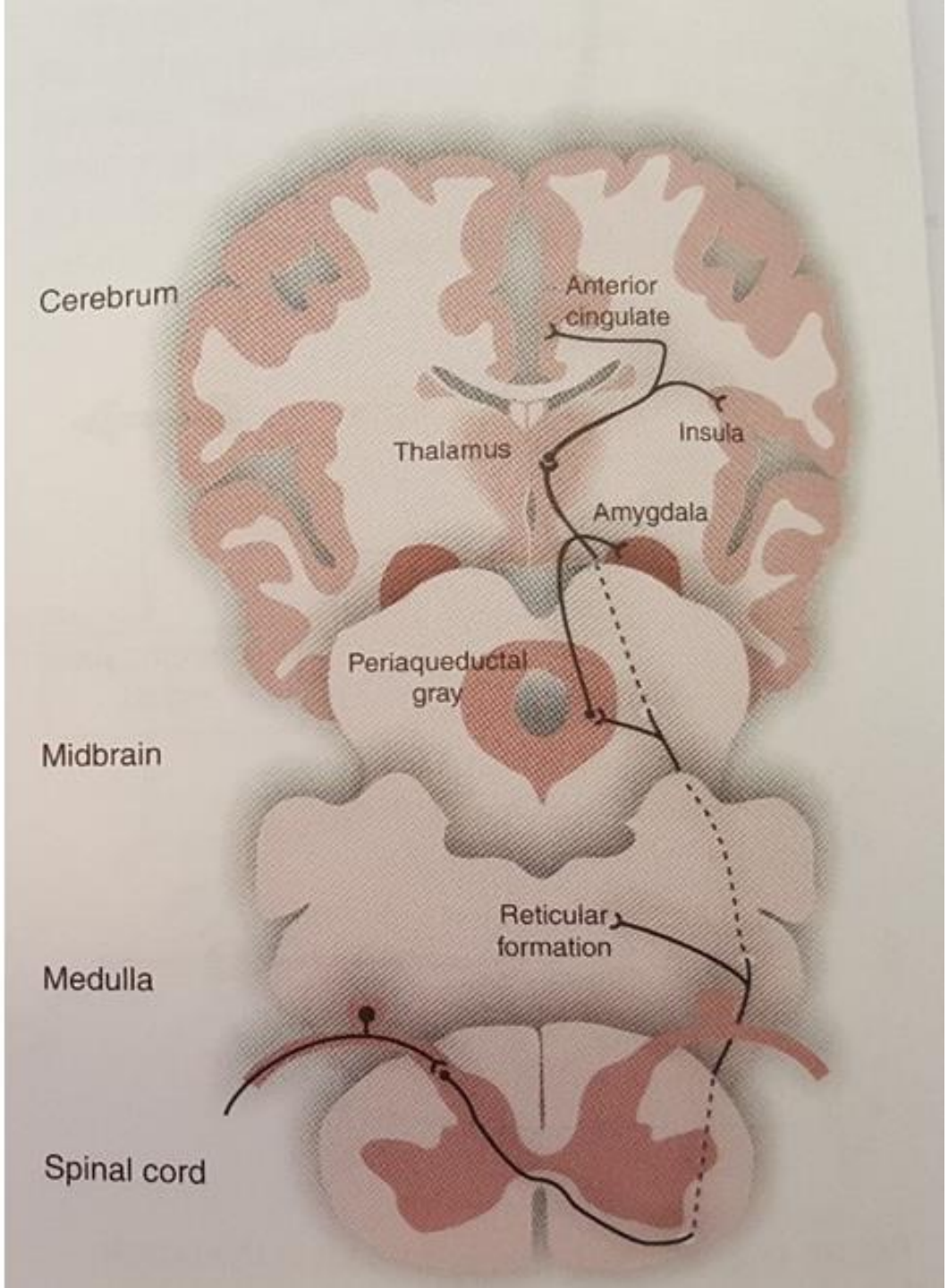
RDoC
Research Domain Criteria Initiative

Medicina de precisão em dor: até onde sabemos



Mecanismos sensitivos / discriminativos

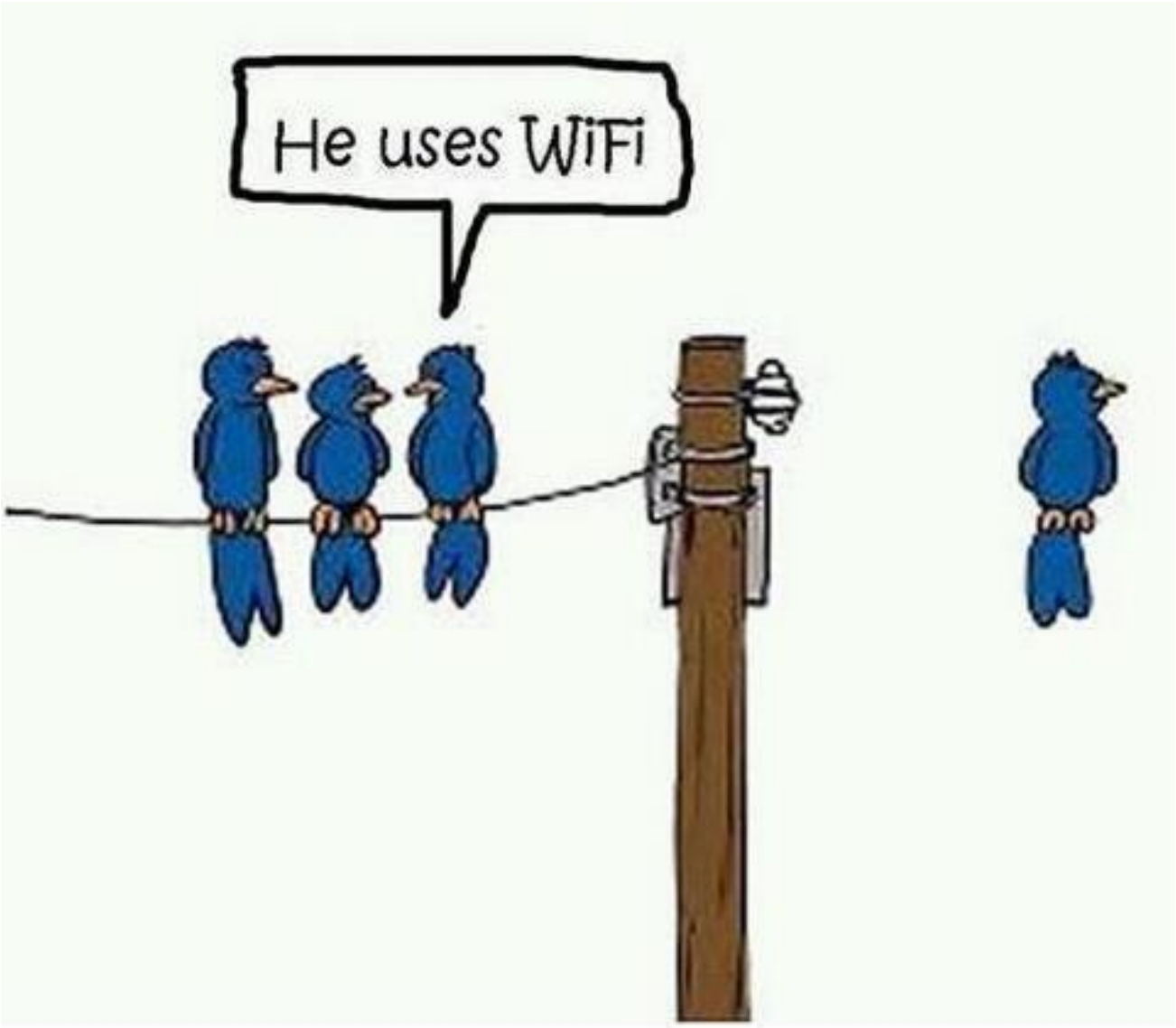
➔ via “tradicional” da dor **“Onde dói?”**



Mecanismos afetivos / motivacionais ➔ formação reticular, substância cinzenta periaqueductal e amigdala **“O quanto dói?”**

Mecanismos cognitivos / interpretativos ➔ Matrix da dor (cíngulo anterior, ínsula e pré-frontal) **“E agora, o que eu faço com a dor?”**

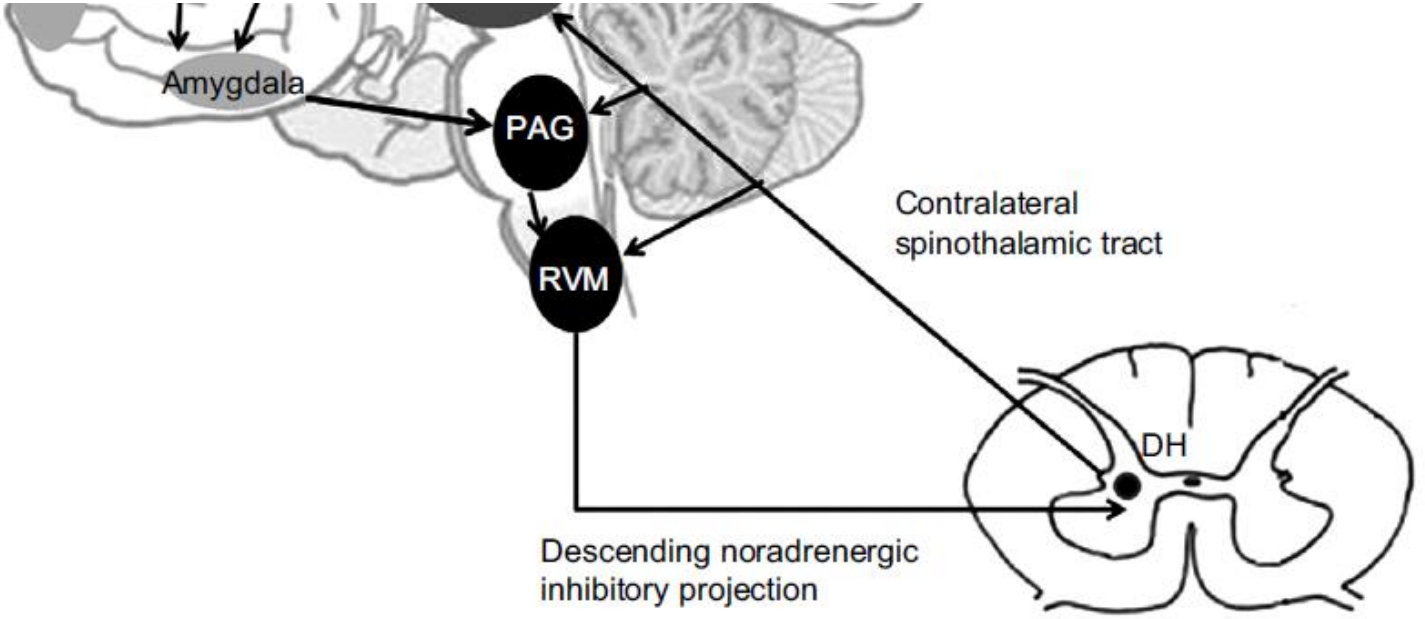
Avanços nas metodologias: neuroimagem e traçadores



Neuroimagem em dor

Brain imaging of pain: state of the art

the cortex.[6] Analysis of experimental pain neuroimaging shows six areas of the brain that consistently respond to acute pain and are believed to play an important role in the sensory-discriminative, cognitive, and affective aspects of pain processing. These are the thalamus, the insular cortex (IC), the primary and secondary somatosensory cortices (SI and SII), the anterior cingulate cortex (ACC), and the prefrontal cortex (PFC).[7] These areas differ depending upon factors such as imaging modality, statistical



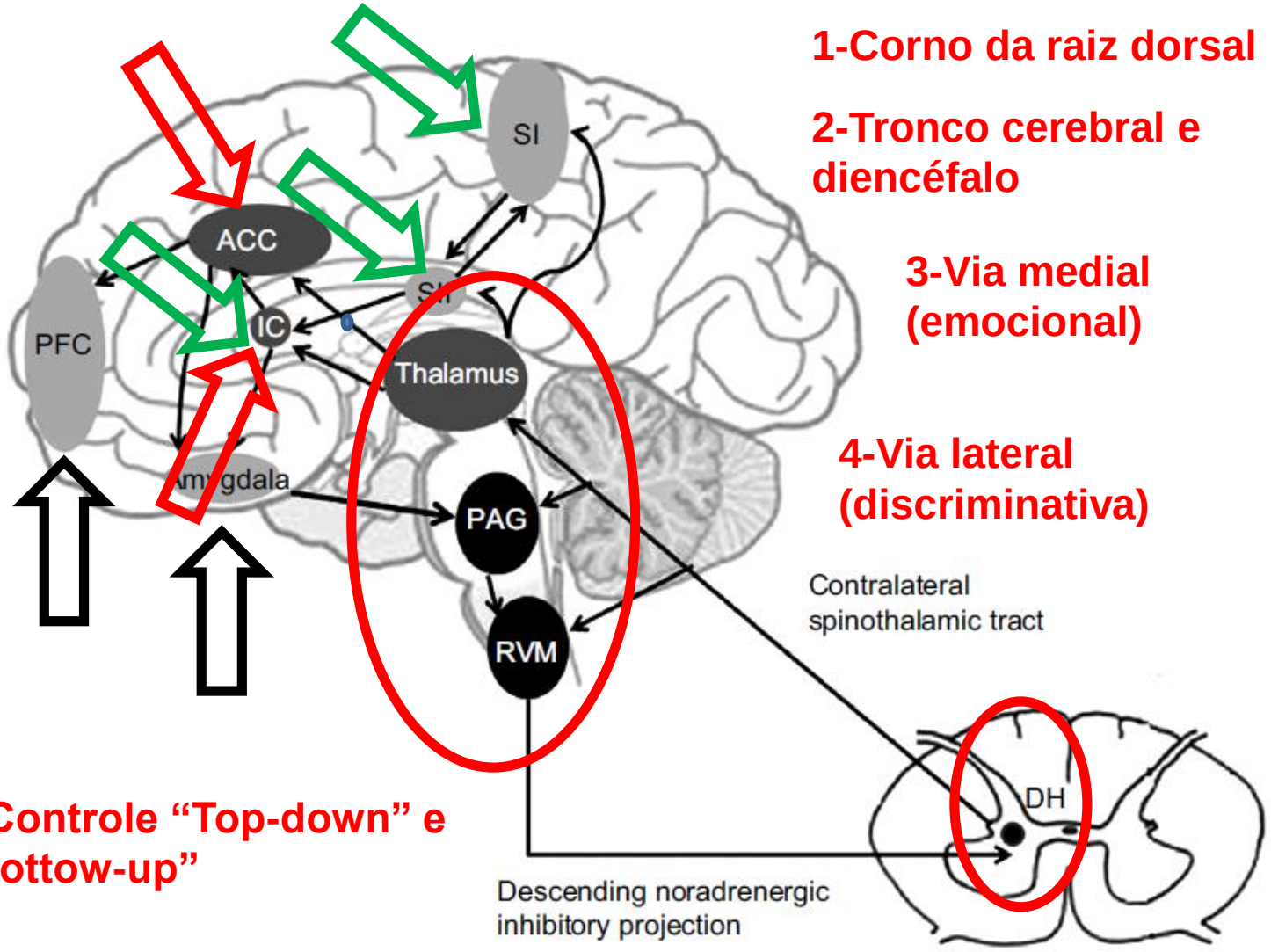
Morton et al., Journal of Pain Research 2016

Brain imaging of pain: state of the art

Functional imaging studies in healthy subjects have revealed a "pain matrix" of structures that can be divided into the medial and lateral pain pathways (Figure 1). The lateral pain pathway is thought to be responsible for the sensory aspects of pain such as location and duration and incorporates SI and SII, parietal operculum (BA7b), and posterior insula.[13,45,46] The activity within the medial pain pathway is associated with the emotional aspects of pain, such as how unpleasant it is. This medial pain system includes the medial nucleus of the thalamus, the anterior insula, Broadmann area 24 of the ACC,[45,47] and the PFC (involved in the cognitive appraisal of a stimulus[48]).

Morton et al., Journal of Pain Research 2016

Brain imaging of pain: state of the art



1-Corno da raiz dorsal

2-Tronco cerebral e diencéfalo

3-Via medial (emocional)

4-Via lateral (discriminativa)

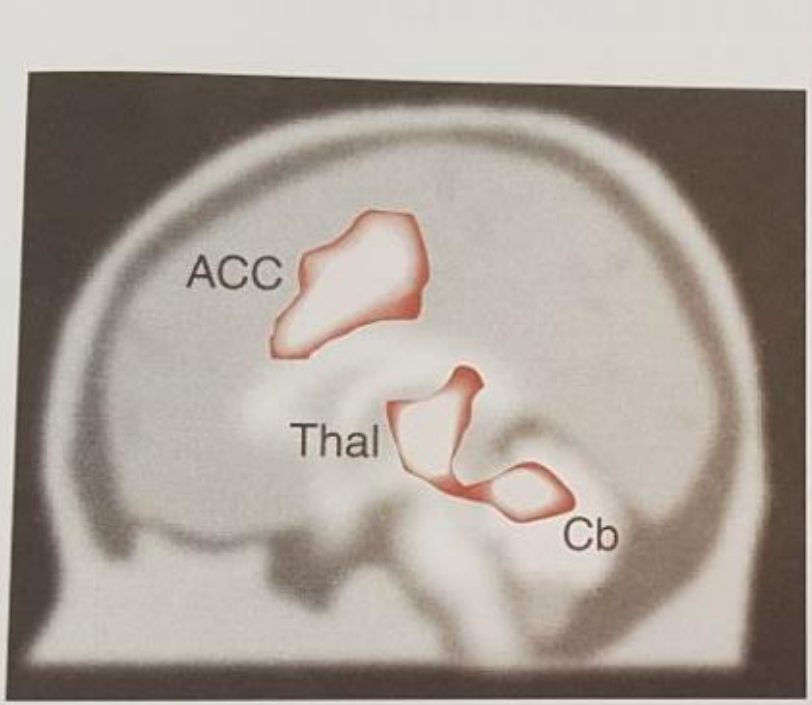
5-Controle "Top-down" e "Bottow-up"

Morton et al., Journal of Pain Research 2016

Várias modalidades demonstrando o conjunto de regiões envolvidas no processamento da dor

A Matrix da Dor

PET-FDG – metabolismo glicolítico



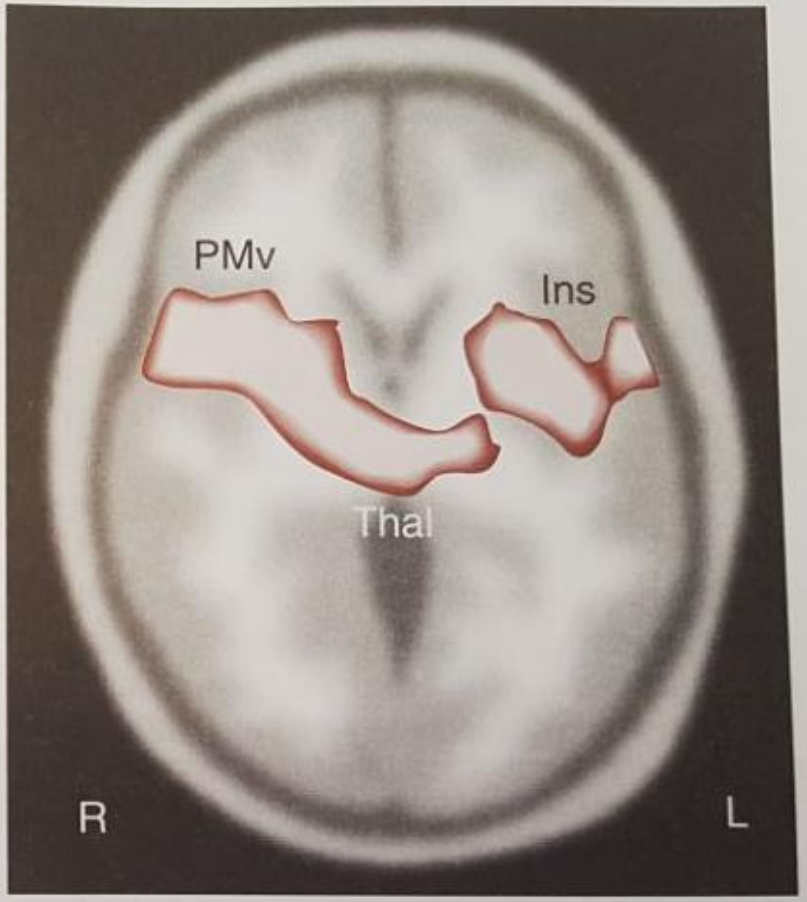


FIGURE 11.7 ● PET scans showing activity in the brain with acute pain. ACC, anterior cingulate cortex; Thal, thalamus; Cb, cerebellum; Ins, insula; PMv, ventral premotor cortex. (Adapted from Coghill RC, McHaffie JG, Yen YF. Neural correlates of interindividual differences in the subjective experience of pain. *Proc Natl Acad Sci U S A*. 2003;100(14):8538-8542.)

PET-com traçadores (opioide)

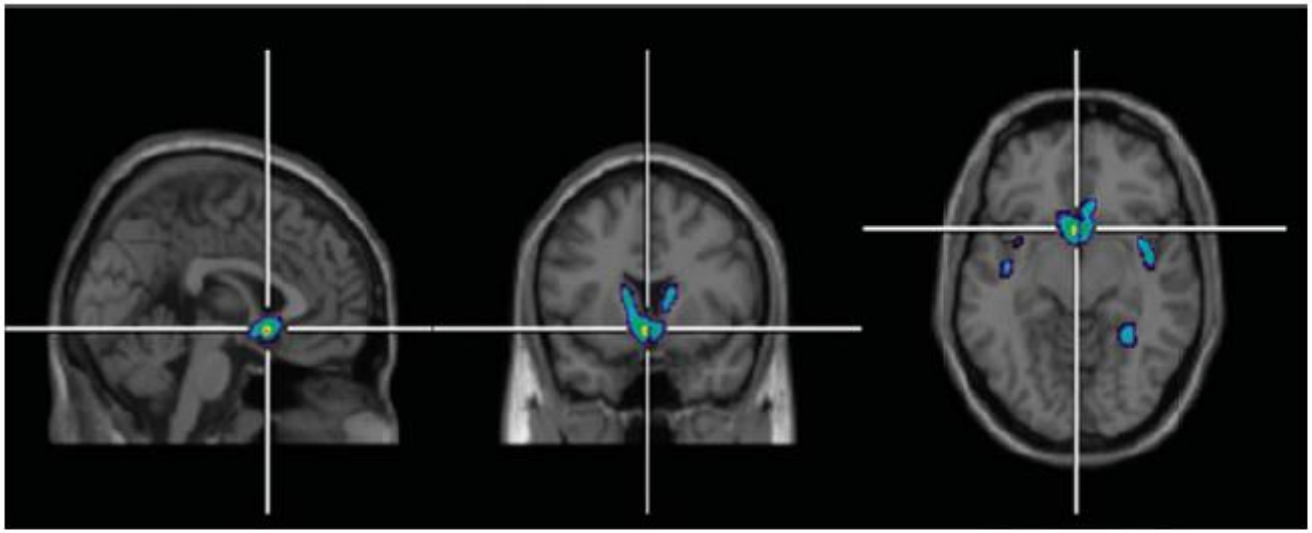
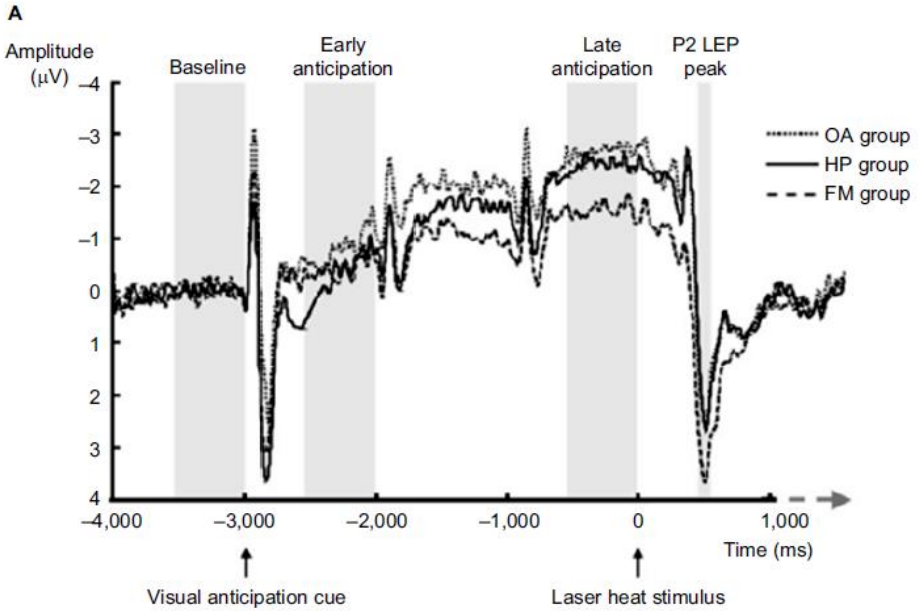


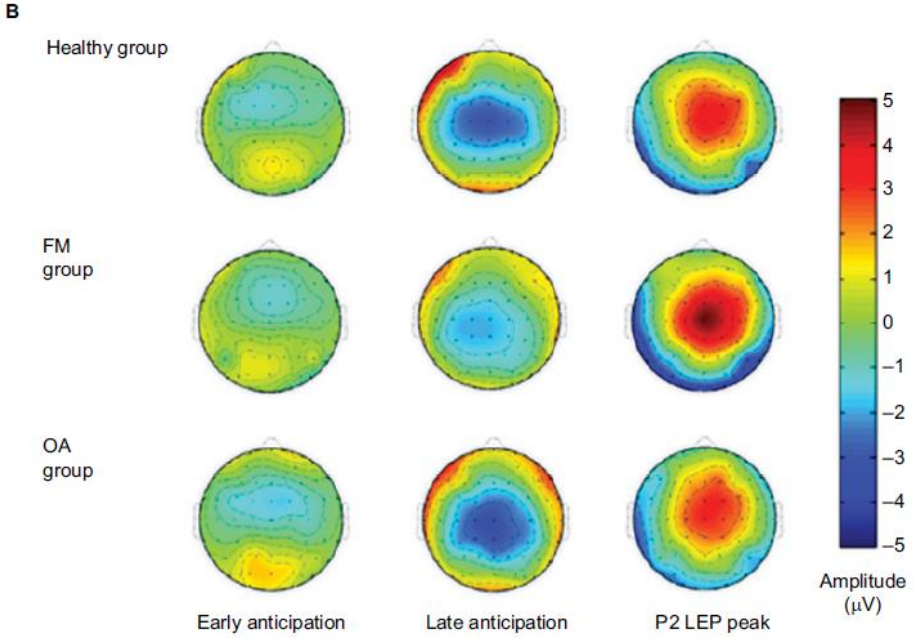
Figure 2 An example figure produced by a neurochemical PET study.

Notes: This diagram was derived from PET imaging of radiotracer ^{11}C-diprenorphine, used to illustrate opioid receptor availability, in patients with OA (n=15) and rheumatoid arthritis (n=2). Regression analysis was performed using the SPM8 software[12] to assess the positive relationship between opioid receptor availability and recent McGill pain scores (as a measure of chronic pain over the past week). This diagram illustrates the positive relationship between chronic pain in these patients and opioid receptor binding in the caudate nucleus, nucleus accumbens, and subcallosal area. The highlighted regions indicate regions of significance.

EEG/ERP – atividade elétrica



Maior resolução temporal (ms), menor resolução espacial



fMRI – BOLD

Brain Mechanisms Supporting Spatial Discrimination of Pain

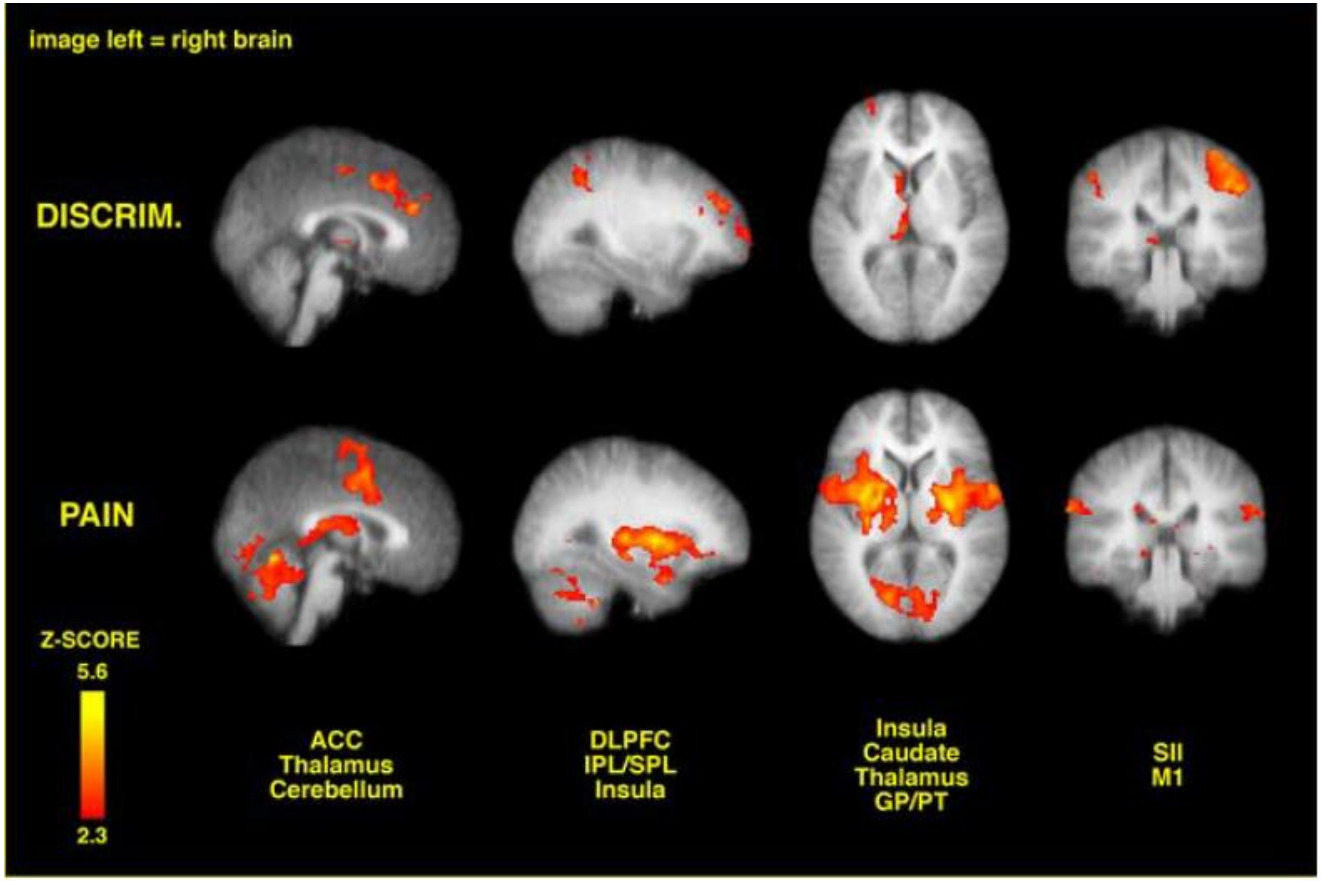


Figure 3. Brain activation related to spatial discrimination of noxious stimuli is distinct from that related to perceived pain. These images are located at $x = 0$ mm, $x = 30$ mm, $z = 5$ mm, and $y = -30$ mm in standard stereotaxic space. IPL/SPL, Inferior parietal lobule/superior parietal lobule; GP/PT, globus pallidus/putamen; M1, primary motor cortex; DISCRIM., discrimination.

Oshiro et al., The Journal of Neuroscience 2007

Forward and reverse inference

Forward inference	Given an induced psychological state	*P(Brain | Psy)* →	We observe brain activity
Reverse inference	Can we infer psychological state?	*P(Psy | Brain)* ←	Given brain activity

Quando os avanços em neuroimagem vão ter repercussão clínica

ORIGINAL ARTICLE

An fMRI-Based Neurologic Signature of Physical Pain

Tor D. Wager, Ph.D., Lauren Y. Atlas, Ph.D., Martin A. Lindquist, Ph.D., Mathieu Roy, Ph.D., Choong-Wan Woo, M.A., and Ethan Kross, Ph.D.

É possível fazer uma inferência reversa em humanos??

Wagner et al., N Engl J Med 2013

"Dor é uma experiência sensitiva e emocional desagradável associada com danos reais ou potenciais em tecidos, ou assim percepcionada como dano.

Fenômeno subjetivo????

International Association for the Study of Pain

O que acontece com a matrix da dor em sujeitos que não sentes dor?

RESEARCH LETTER

The "Pain Matrix" in Pain-Free Individuals

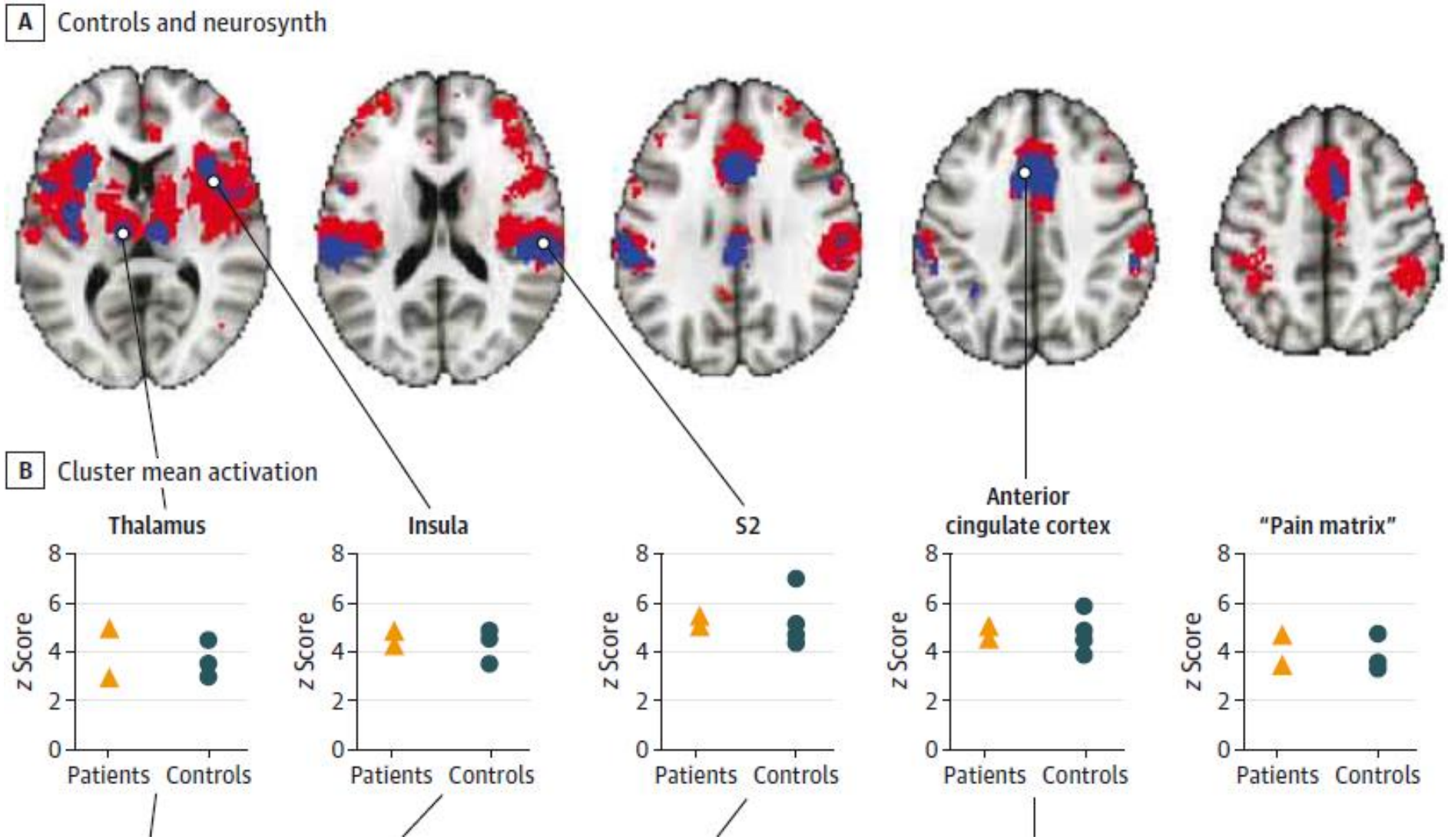
Human functional imaging provides a correlative picture of brain activity during pain. A particular set of central nervous system structures (eg, the anterior cingulate cortex, thalamus, and insula) consistently respond to transient nociceptive stimuli causing pain. Activation of this so-called *pain matrix* or *pain signature* has been related to perceived pain intensity, both within and between individuals,[1,2]

Editorial

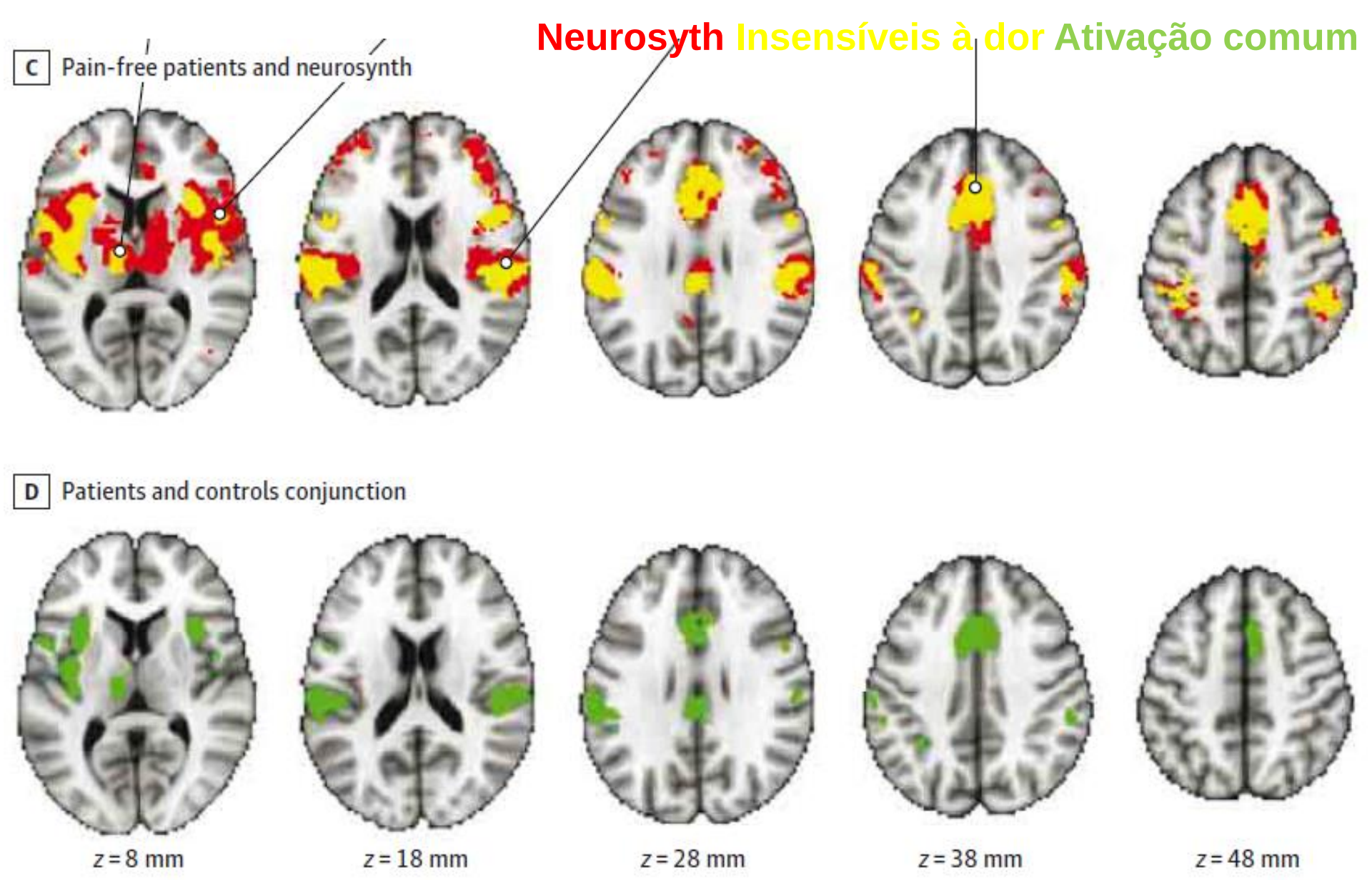
ity with fMRI. Loss-of-function *SCN9A* mutations in these individuals abolishes sensory neuron sodium channel Nav1.7 activity, resulting in pain insensitivity through an impaired peripheral drive that leaves tactile percepts fully intact.[5] This allows complete experimental disambiguation of sensory responses and painful sensations.

Salomons et al., JAMA neurol 2016

Neurosyth Controles Insensíveis à dor



N = 6 (4 controles e 2 insensíveis à dor) **Salomons et al., JAMA neurol 2016**



N = 6 (4 controles e 2 insensíveis à dor) **Salomons et al., JAMA neurol 2016**

Discussion | Previous work[3] interpreting pain matrix activation as a response to salient sensory stimuli rather than perceptual qualities unique to pain has been challenged on the basis that the presence of pain in response to these stimuli could not be fully ruled out.[4] In this study, we addressed this challenge by demonstrating intact pain matrix responses in individuals congenitally unable to experience pain.

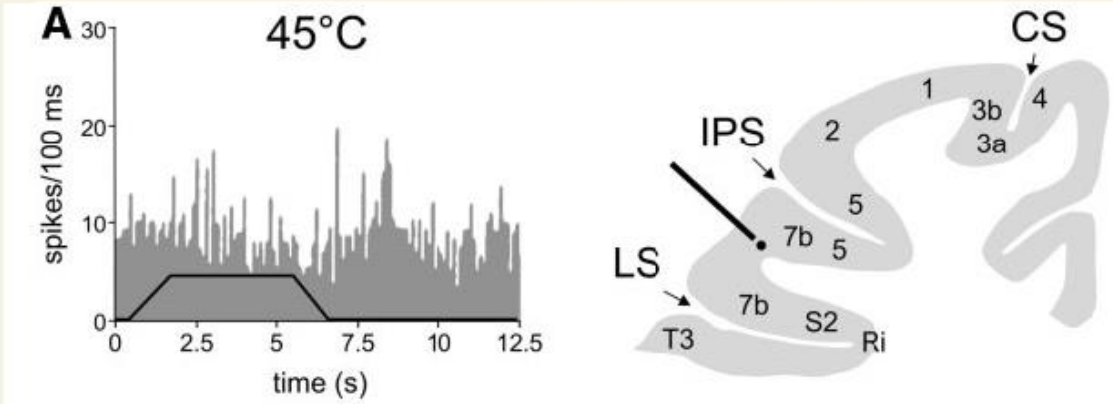
These observations reinforce the need for caution in using pain matrix responses for diagnosis or drug discovery and corroborate evidence that reported correlations between neuroimaging data and perceived pain have largely relied on non-pain-specific activities.[3] Examining how the brain gives rise to the unique perceptual experience of pain will require human neuroimaging to be supplemented by techniques that allow for causal inferences. These include studies in nonhuman species where cell populations and circuitry can be genetically or chemically modified[5] and human studies of individuals with relevant lesions or genetic mutations.

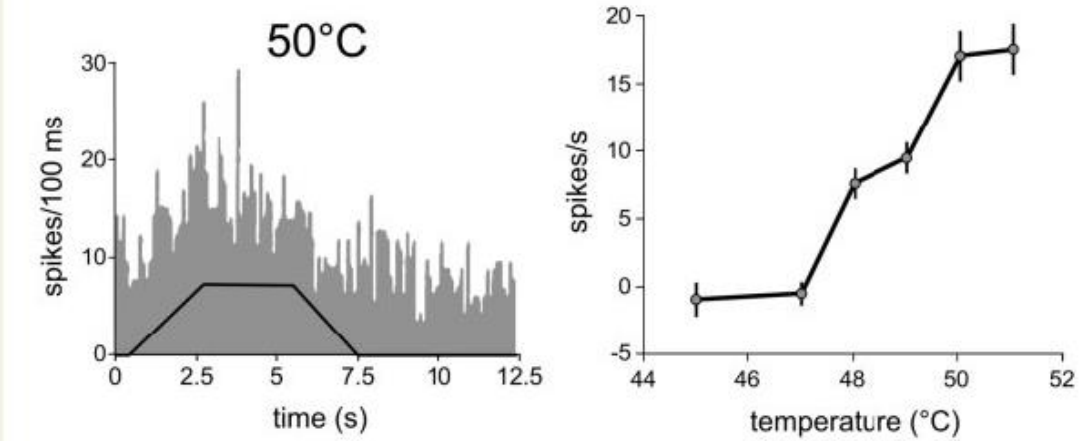
The search for pain biomarkers in the human brain

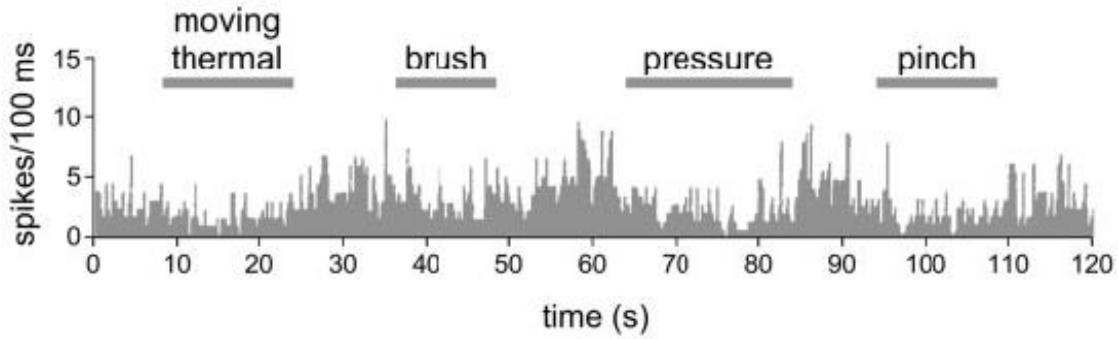
Neurônios seletivos e específicos para processamento da dor? Matrix de dor é uma matrix seletiva ou específica para dor?

Sistema ativado em estímulos não dolorosos salientes, desagradáveis e relevantes para o contexto atual.

Mouraux & Iannetti, Brain 2018



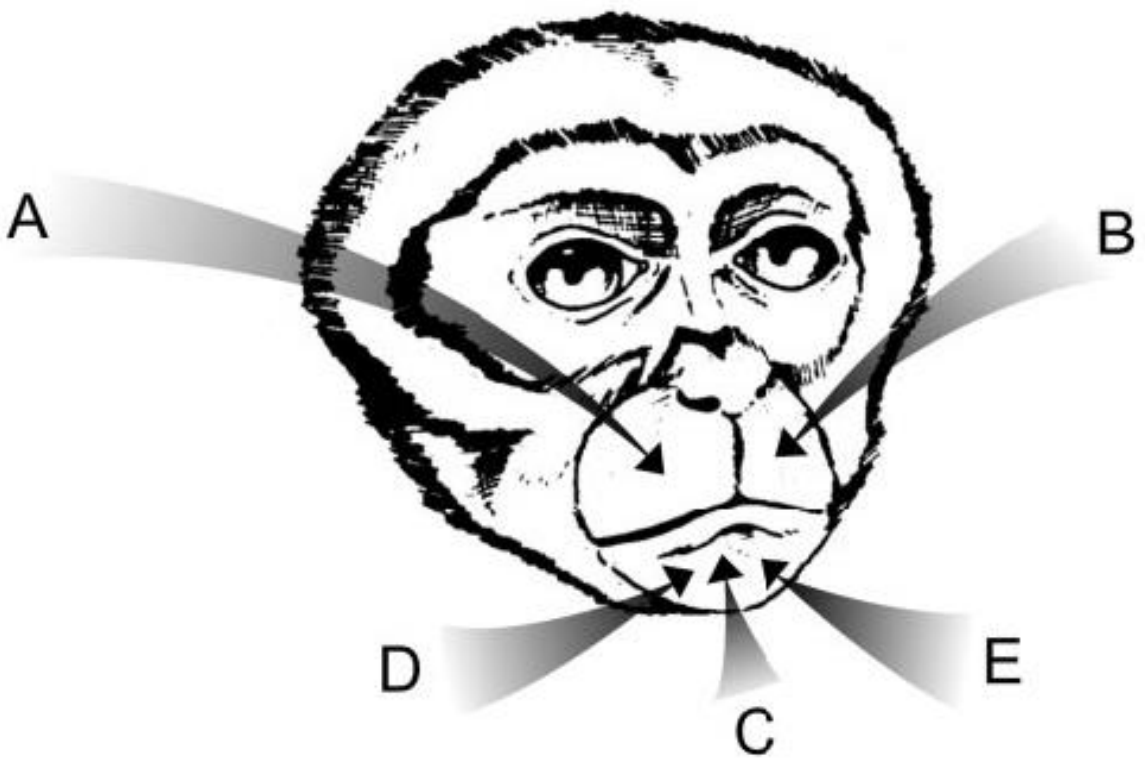




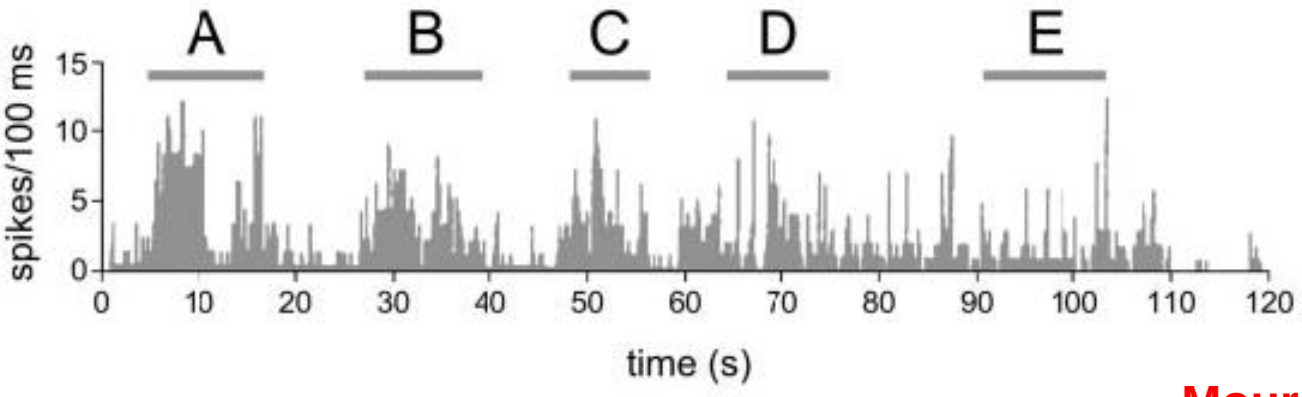
Neurônios que respondem a dor e respondem a estímulos táteis não-dolorosos

CS = central sulcus; IPS = intraparietal sulcus; LS = lateral sulcus

Mouraux & Iannetti, Brain 2018

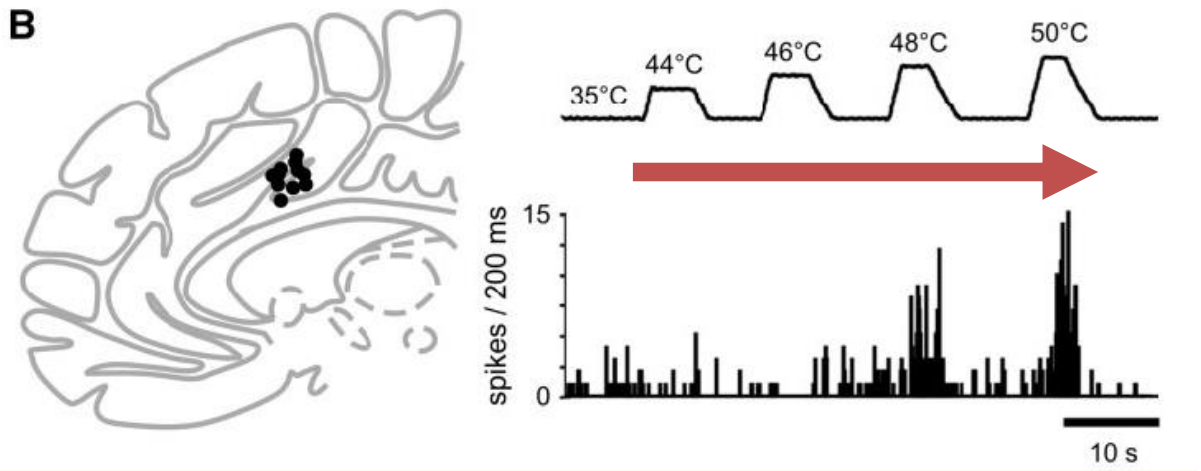


Resposta neuronal a estímulos visuais que se aproximavam dos locais indicados (principalmente novos ou ameaçadores)



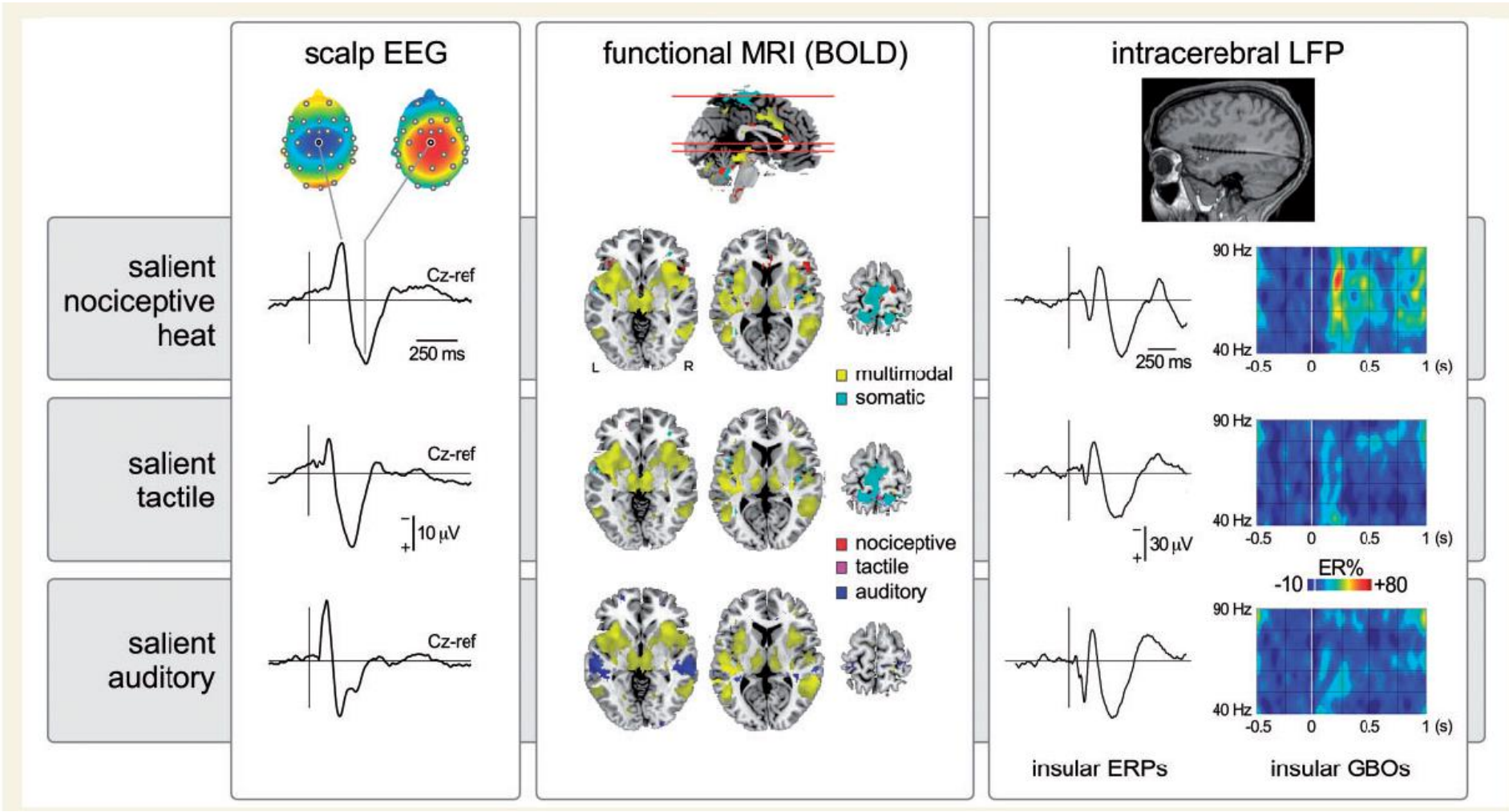
Mouraux & Iannetti, Brain 2018

Resposta neuronal do cíngulo anterior a estímulos dolorosos e ao observar o examinador receber estímulos dolorosos



Mouraux & Iannetti, Brain 2018

A resposta neuronal induzida pela dor não é específica ou seletiva para a dor. Componentes da "rede de saliência".



Local field potentials (LFPs)

Mouraux & Iannetti, Brain 2018

Neurocognitive aspects of pain perception

Relação intima entre emoção e dor
Processamento compartilhado (matriz da dor não é específica – ausência do "córtex da dor")

Wiech & Tracey et al., Trends Cogn Sci. 2008

Morte vodu: a importância da interação corpo e cérebro.

KEYNOTE ADDRESS

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'Voodoo' death revisited: The modern lessons of neurocardiology†

In 1942, Walter Bradford Cannon published a remarkable paper entitled "'Voodoo' Death,"[1] in which he recounted anecdotal experiences, largely from the anthropology literature, of death from fright. These events, drawn from widely disparate parts of the world, had several features in common. They were all induced by an absolute belief that an external force, such as a wizard or medicine man, could, at will, cause demise and that the victim himself had no power to alter this course. This perceived lack of control over a powerful external force is the *sine qua non* for all the cases recounted by Cannon, who postulated that death was caused "by a lasting and intense action of the sympathico-adrenal system." Cannon believed that this phenomenon was limited to soct, that they feel themselves bewildered strangers in a hostile world. Instead of knowledge, they have fertile and unrestricted imaginations which fill their environment with all manner of evil spirits capable of affecting their lives disastrously."

personal danger or threat of injury; (7) after danger is over; and (8) reunion, triumph, or happy ending. Common to all is that they involve events impossible for the victim to ignore and to which the response is overwhelming excitation, giving up, or both.

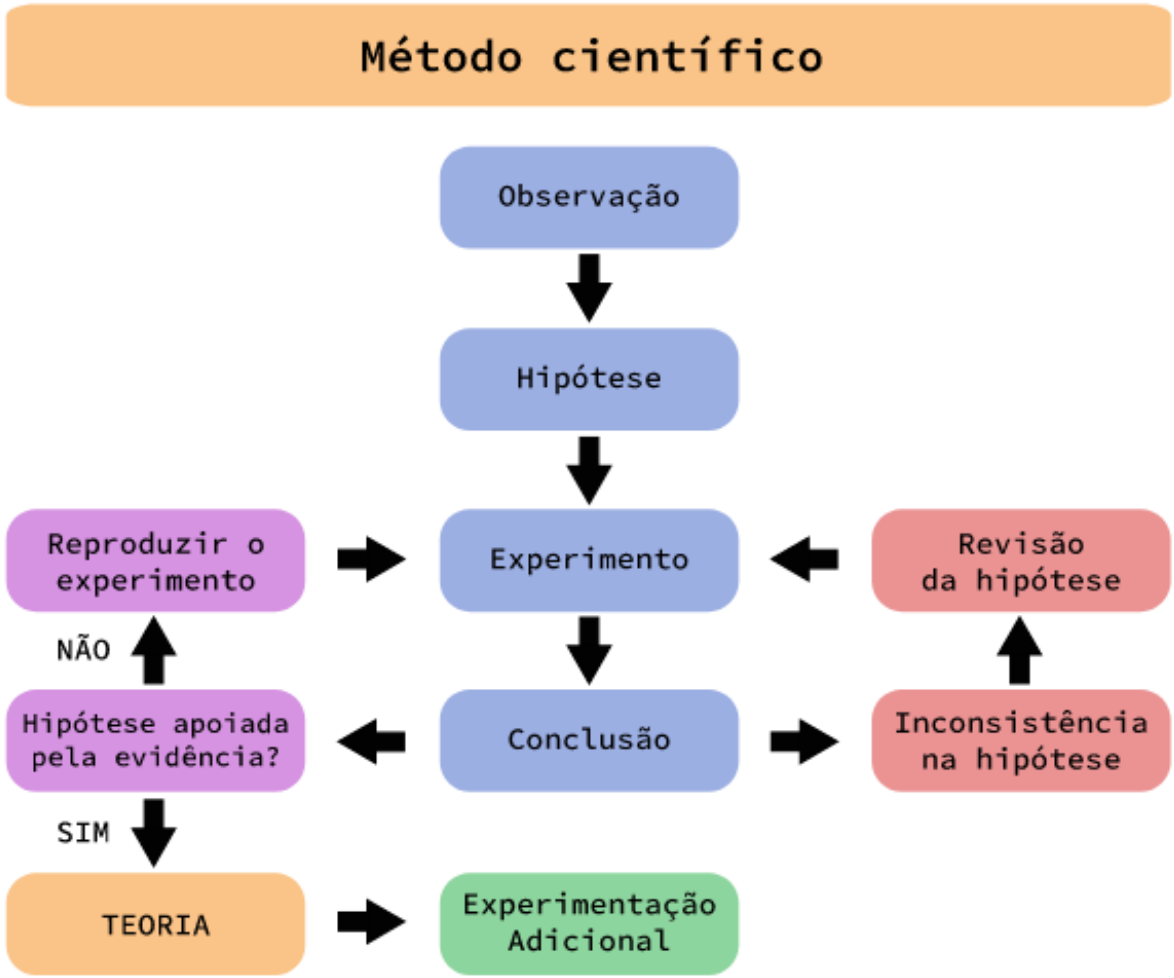
In 1957, Carl Richter reported on a series of experiments aimed at elucidating the mechanism of Cannon's "voodoo" death.[1] Richter studied the length of time domesticated rats could swim at various water temperatures and found that at a water temperature of 93° these rats could swim for 60 to 80 minutes. However, if the animal's whiskers were trimmed, it would invariably drown within a few minutes. When carrying out similar experiments with fierce, wild rats, Richter noted that a number of factors contributed to the tendency for sudden death, the most important of which were the restraint involved in holding the animals and confinement in the glass swimming jar with no chance of escape. Trimming the rats' whiskers,

Martin A. Samuels
cardiologyonline.com

Um modelo científico é uma idealização simplificada de um sistema que possui maior complexidade, mas que ainda assim supostamente reproduz na sua essência o comportamento do sistema complexo que é o alvo de estudo e entendimento.

➔ representação abstrata, conceitual, gráfica ou visual

➔ essencial de qualquer atividade científica.



Fluxograma do método científico

Efeito placebo: um modelo de estudo dos fenômenos mentais de cura.

Placebo é qualquer substância ou tratamento inerte (ou seja, que não apresenta interação com o organismo) empregado como se fosse ativo. **Efeito placebo** é quando essa substância ou procedimento produz um **efeito** fisiológico positivo, mesmo que não tenha capacidade para isso, melhorando os sintomas.

➔ Dor, regulação autonômica e do sistema imune
➔ Gerada pelo próprio cérebro

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Allan H. Ropper, M.D., *Editor*

Placebo and Nocebo Effects

Luana Colloca, M.D., Ph.D., and Arthur J. Barsky, M.D.

- Comum na prática clínica
- Fundamental considerar o efeito placebo no desenvolvimento de novas medicações
- Parte do arsenal terapêutico

Colloca & Barsky, N Engl J Med 2020

Importância na prática clínica e em pesquisa

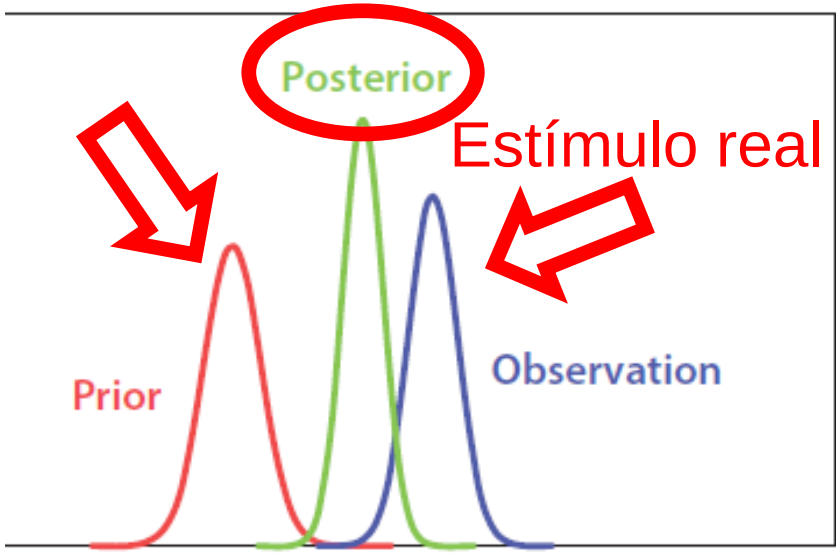
- Expectativa e sugestão
- Mecanismos de aprendizado associativo
- “open-label placebo”
- Quantificar o lessebo nos estudos clínicos
- Predição de nocebo

Colloca & Barsky, N Engl J Med 2020

The Cognitive Neuroscience of Placebo Effects: Concepts, Predictions, and Physiology

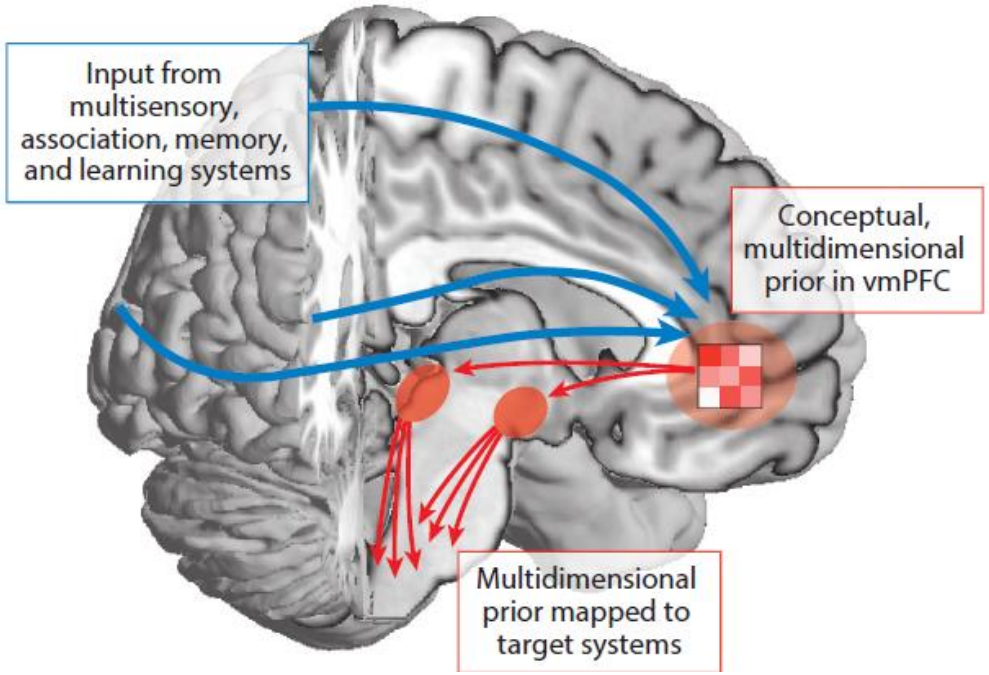
- Expectativa (predição)
- Aprendizado associativo
- Contexto pessoal e social

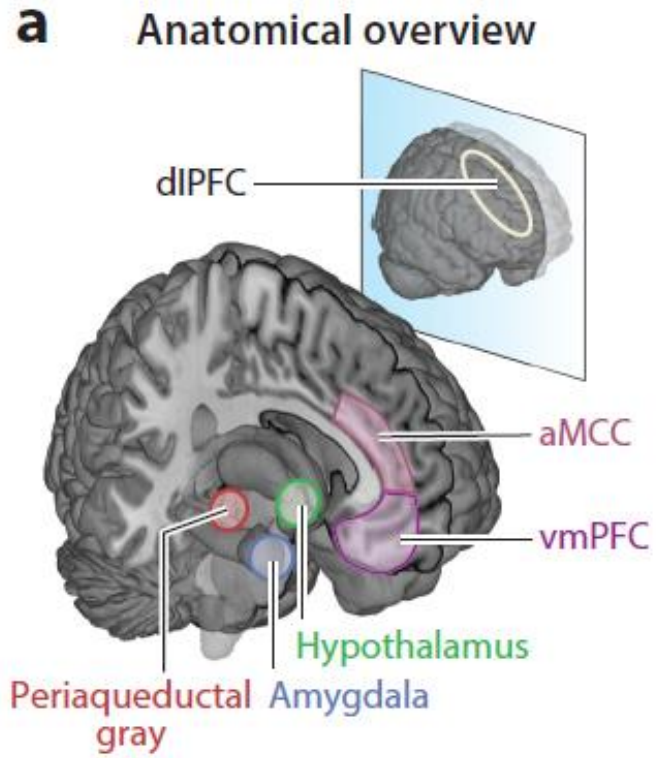
(acreditar, ter fé)



Geuter et al., Annu. Rev. Neurosci. 2017

Controle dos mecanismos automáticos

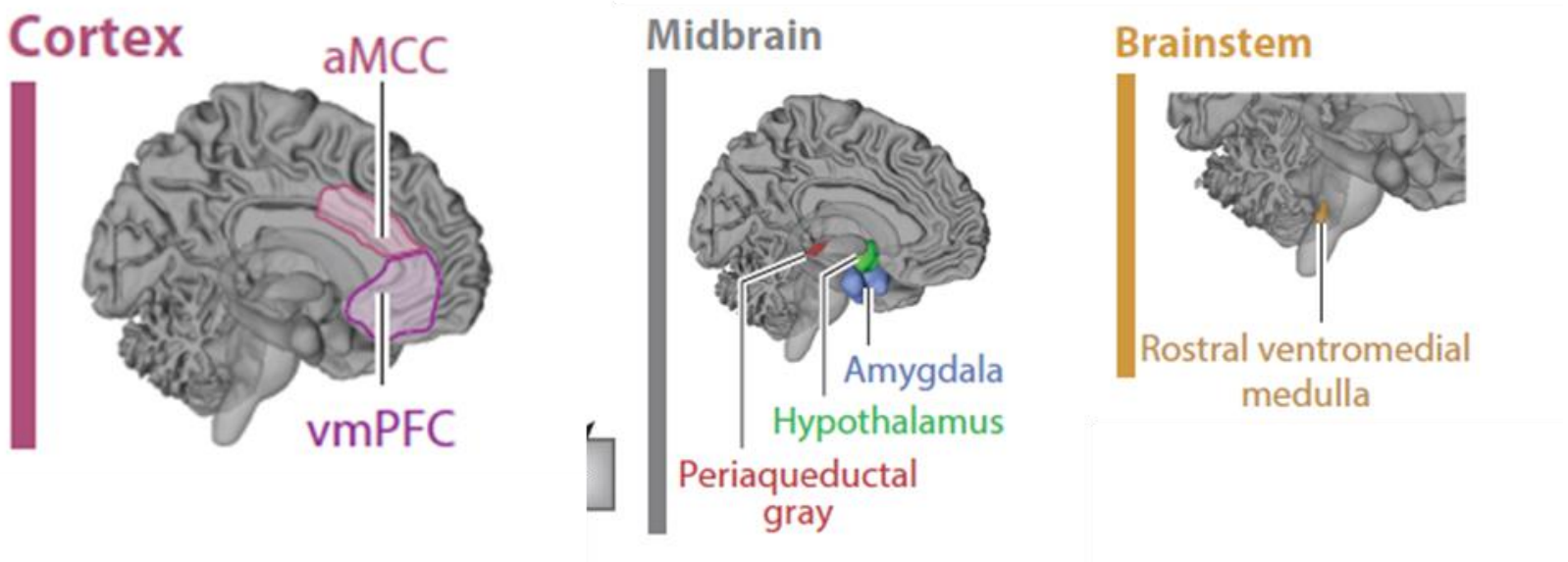




Geuter et al., Annu. Rev. Neurosci. 2017

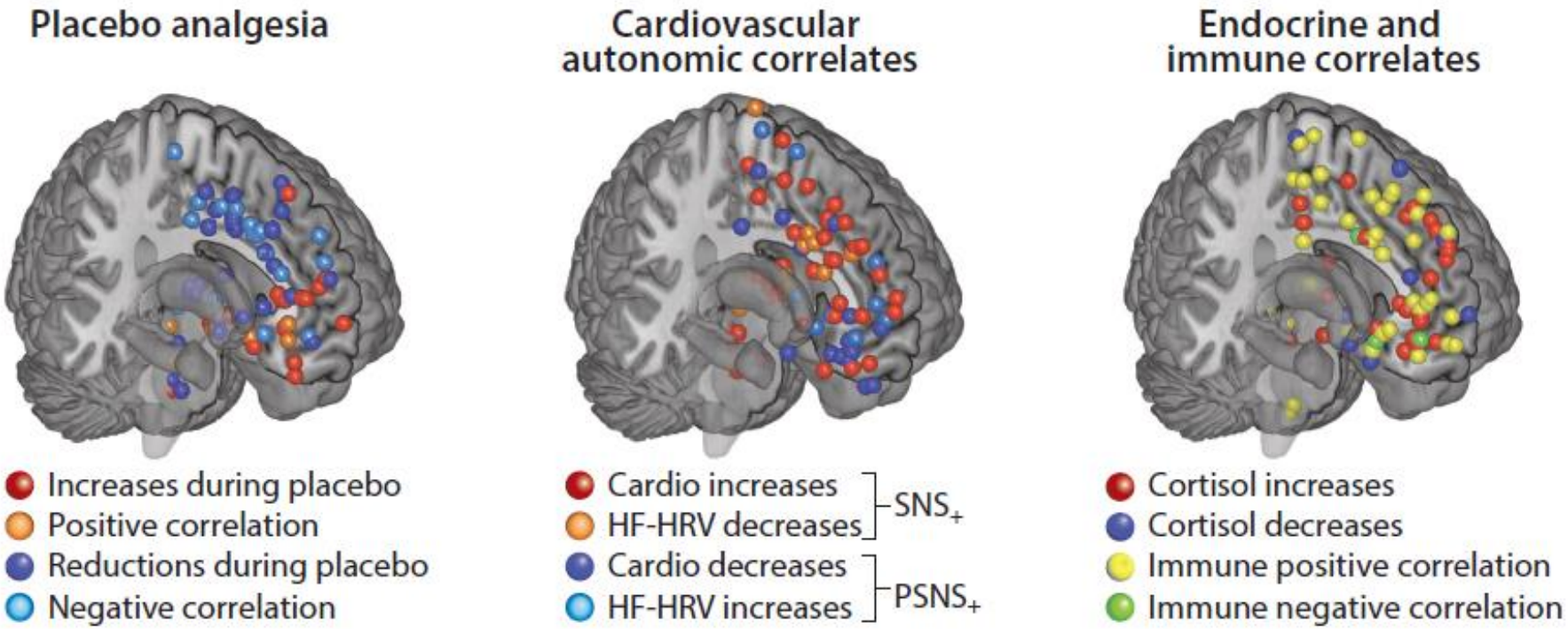
Controle dos mecanismos automáticos

Regiões de controle ⟶ **Regiões controladas**

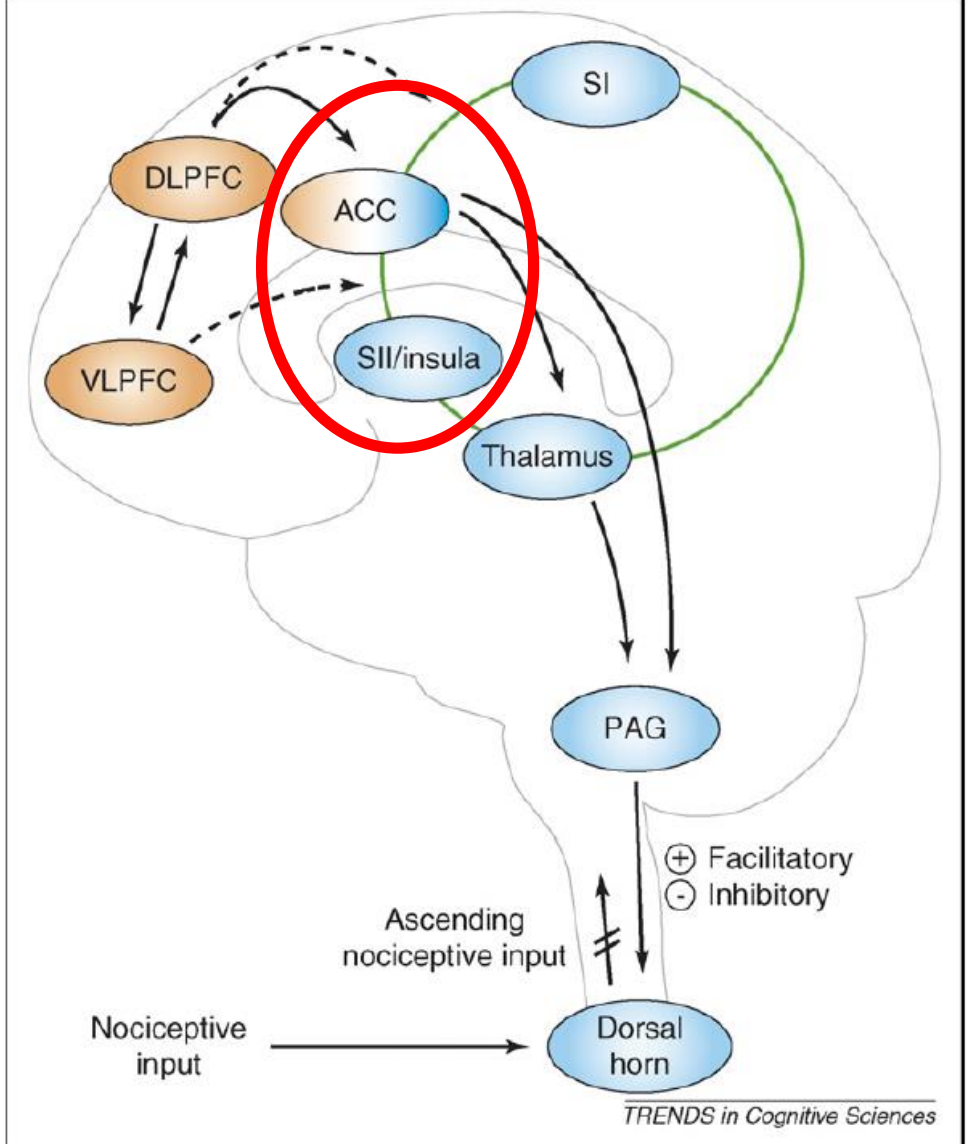


Geuter et al., Annu. Rev. Neurosci. 2017

O que acontece durante o palcebo



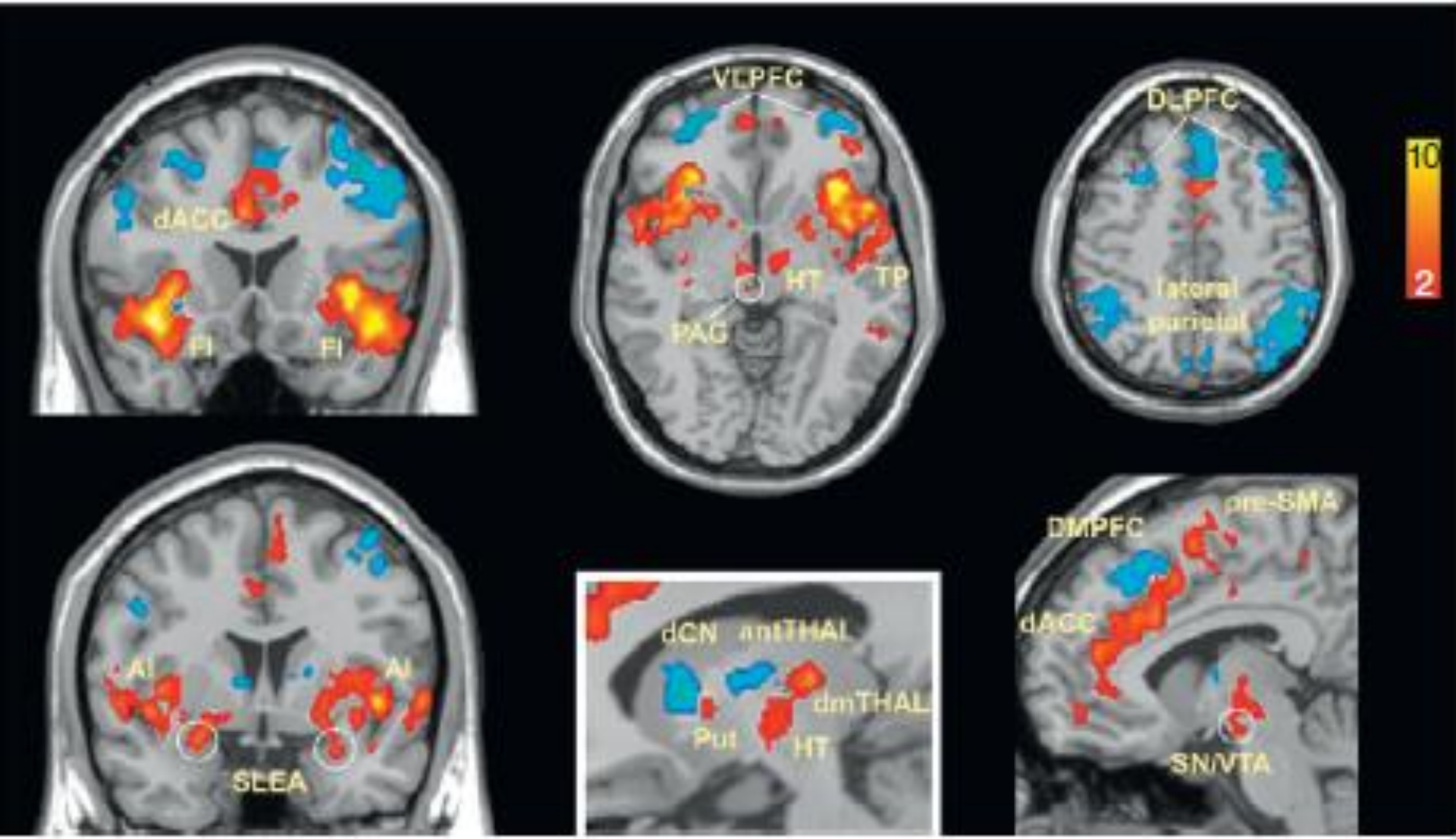
Geuter et al., Annu. Rev. Neurosci. 2017



ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PAG, periaqueductual gray; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; VLPFC, ventrolateral prefrontal cortex.

Wiech & Tracey. Trends Cogn Sci. 2008

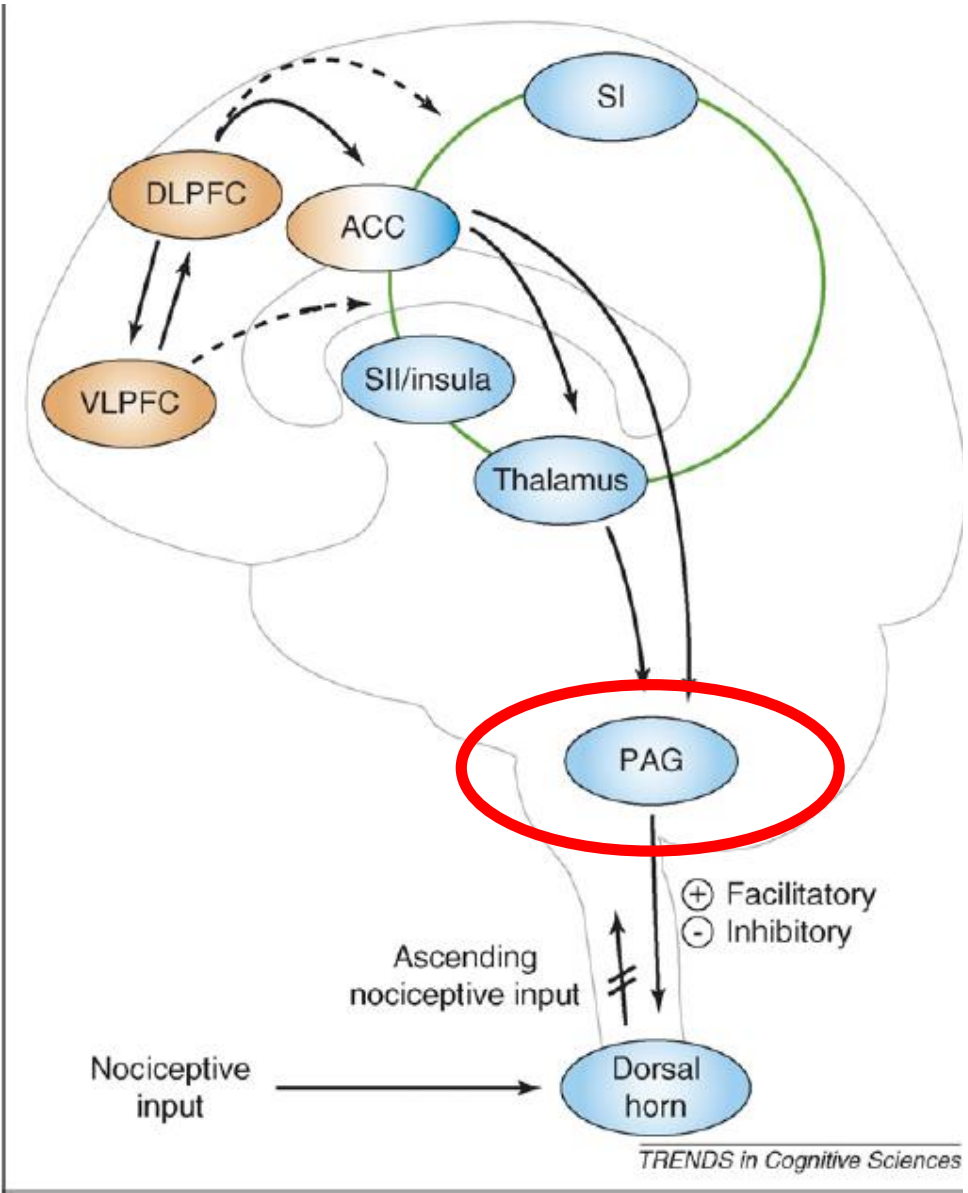
Rede de Saliência



Menon V. Salience Network. In: Arthur W. Toga, editor. Brain Mapping: An Encyclopedic Reference.

The Cerebral Signature for Pain Perception and Its Modulation

Neuron 55, August 2, 2007



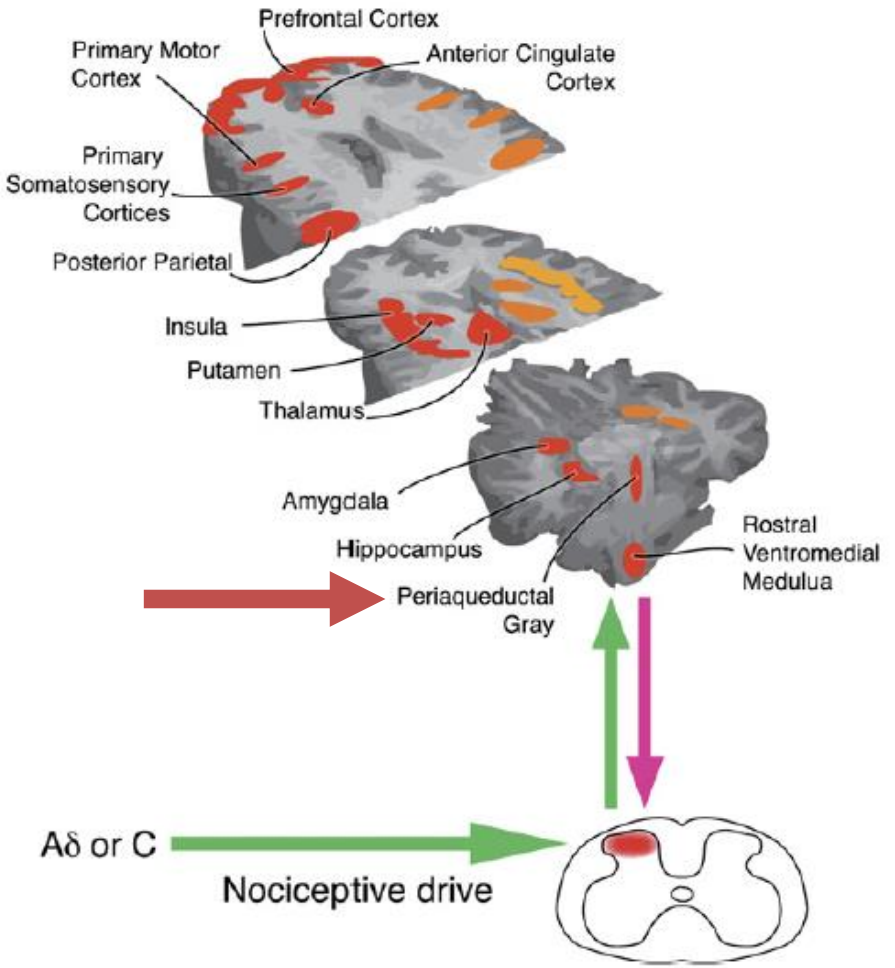
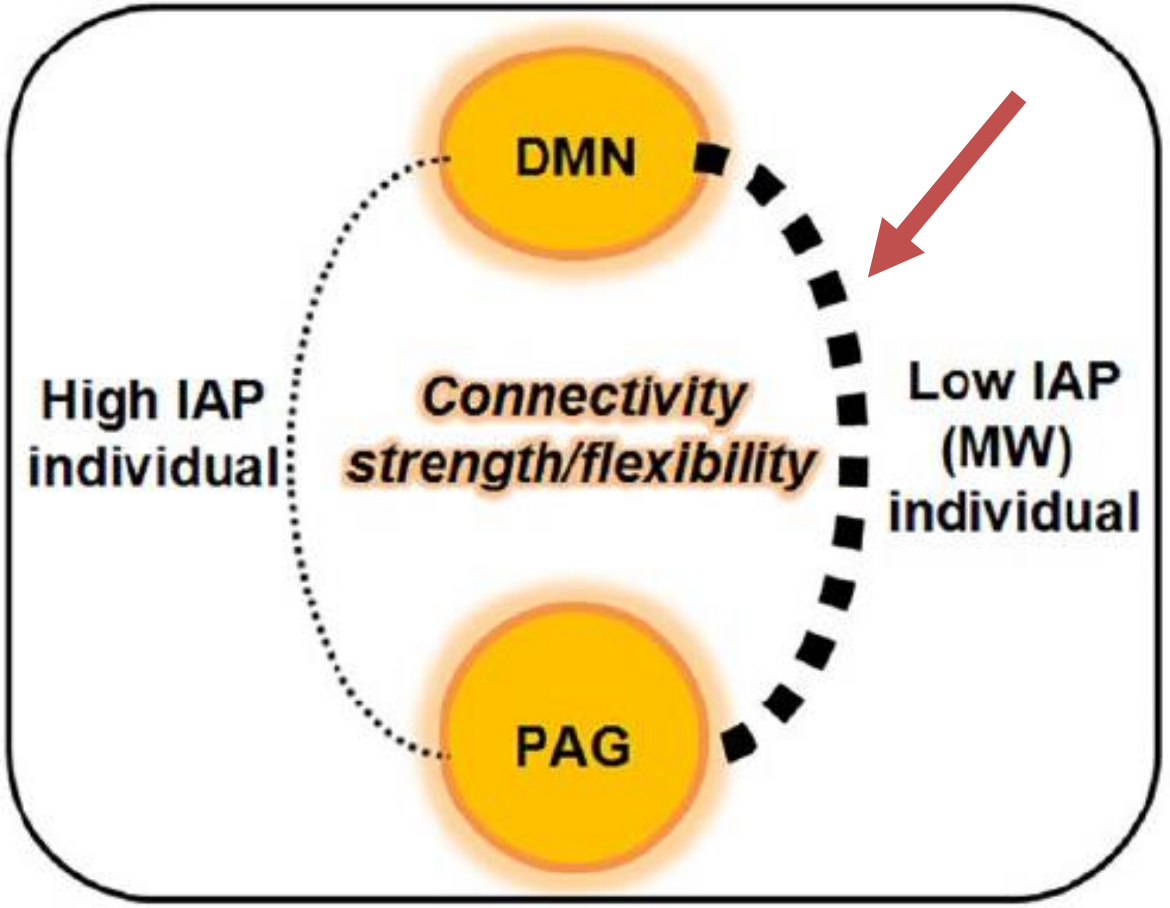


Figure 2. Neuroanatomy of Pain Processing

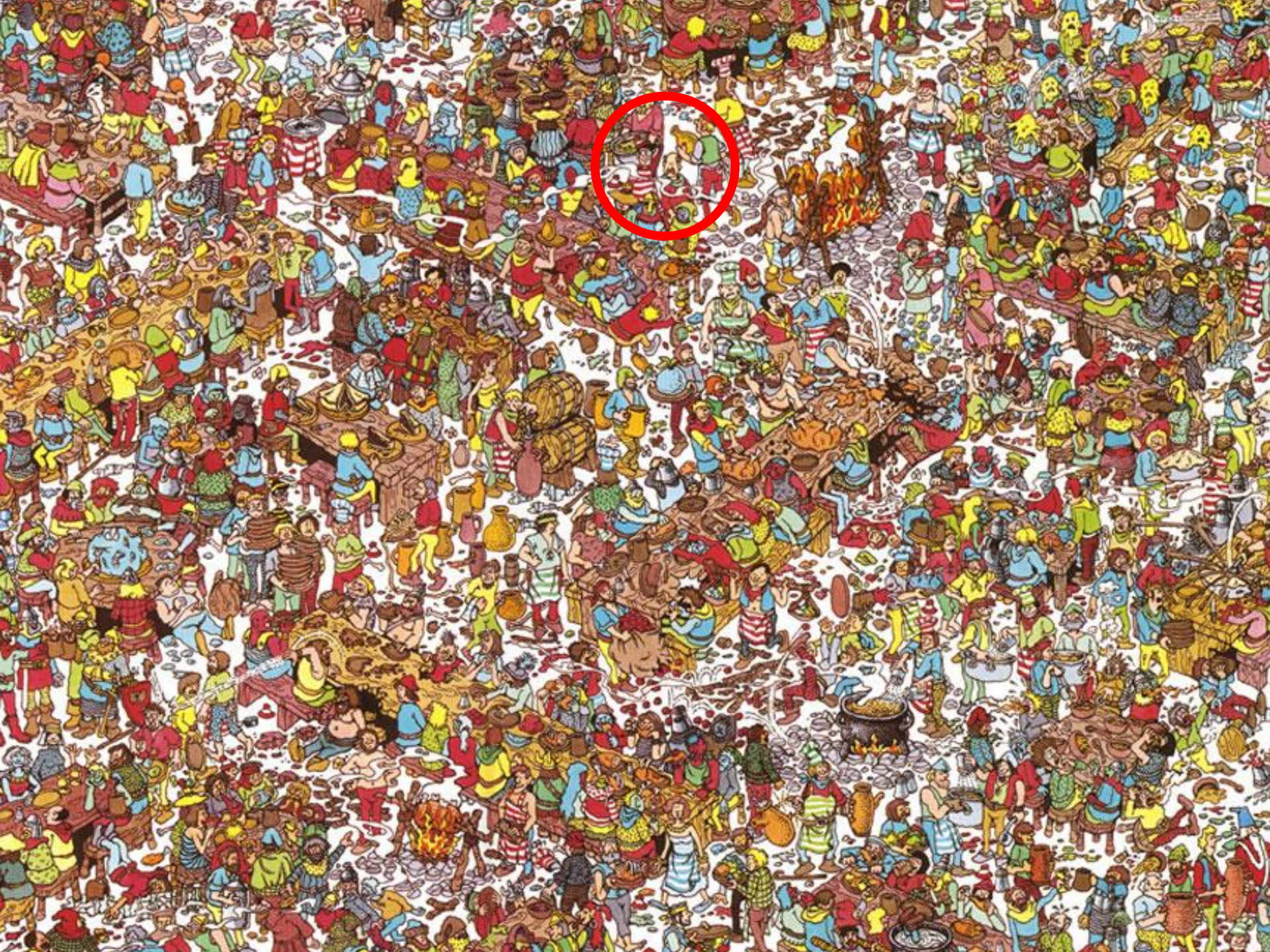
Main brain regions that activate during a painful experience, highlighted as bilaterally active but with increased activation on the contralateral hemisphere (orange).

The Neural Code for Pain: From Single-Cell Electrophysiology to the Dynamic Pain Connectome



Intrinsic attention to pain (IAP) (i.e., tendency to spontaneous focus on or away from pain) in structural and functional connectivity between DMN and periaqueductal gray (PAG).

Kucyi & Davis. Neuroscientist 2016



Muito obrigado

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