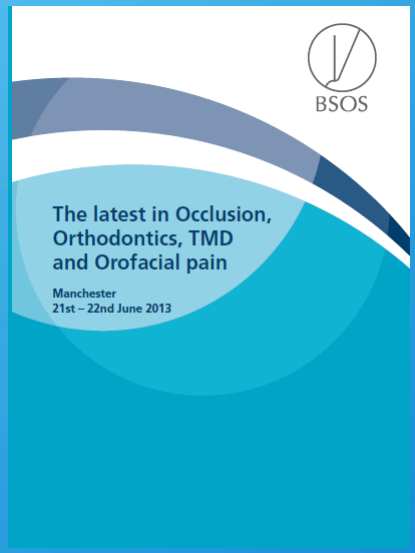
KING'S College LONDON

Orofacial pain: what's new?

BSOS 1 June 2013

Manchester



Tara.renton@kcl.ac.uk

‘pain is inevitable, suffering is optional’

The report, "**Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research,**" says the nation's health care system has largely failed Americans in pain and calls for a "cultural transformation" of the way in which the United States approaches and manages patients with pain.

"**A third of the nation experiences chronic pain**. ... Costing us more than we pay as a nation on cardiovascular disease and cancer,"

Chronic pain costs the US up to $635 billion each year in medical treatment and lost productivity. *The 2010 Patient Protection and Affordable Care Act* required the Department of Health and Human Services (HHS) to enlist the IOM in examining pain as a public health problem.

- Institute of medicine USA 2011 report on pain

Chronic pain: Consequences UK

- 33% of UK population suffer
- 13% work force is compromised
- Diabetic and HIV neuropathy
- Accounts for £40 billion year UK

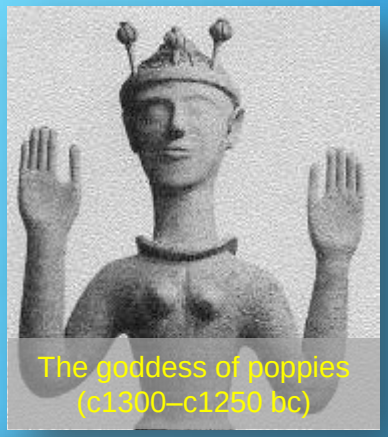
An update

What is pain?

- Mechanisms

Orofacial pain

Understanding pain


The goddess of poppies (c1300–c1250 bc)

- Galen (129-216), who described a network of nerves leading to the brain

- Mainonides (1138-1204):
  Galens art heals only the body but
  Abou Amrans heals the body and soul'

- Descartes (1596-1650) who first stated that pain was experienced in the brain, rather than in the heart as was the accepted Aristotelian doctrine

Pain is complex

- Nociception
- Sensation
- Behaviour
- Suffering

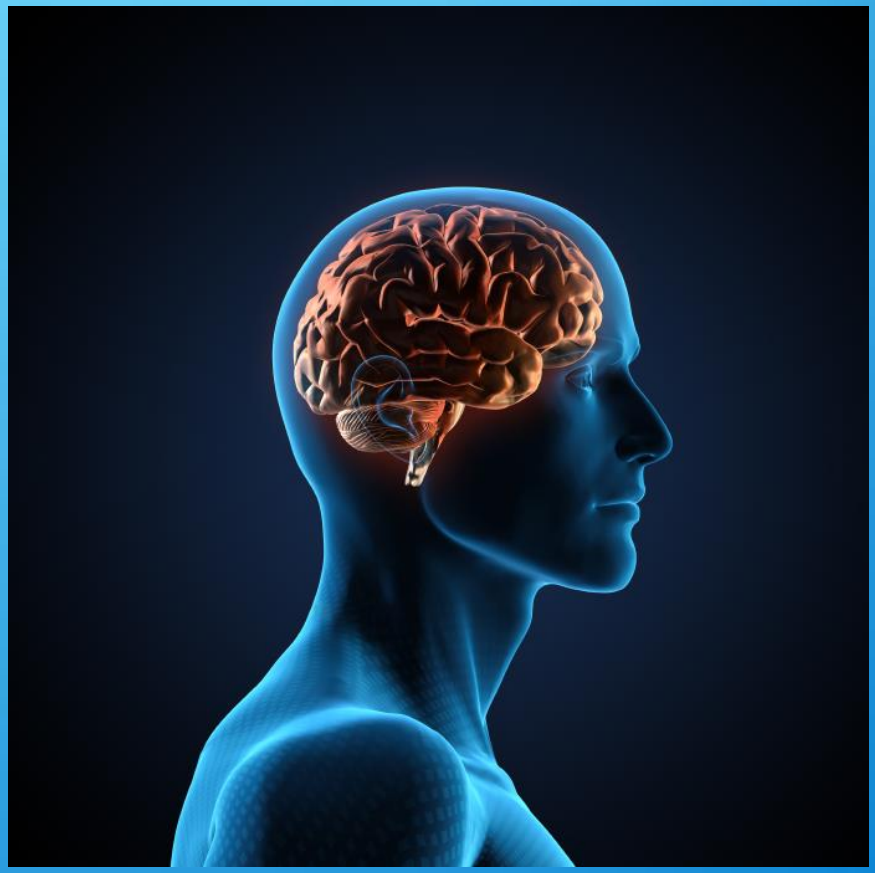
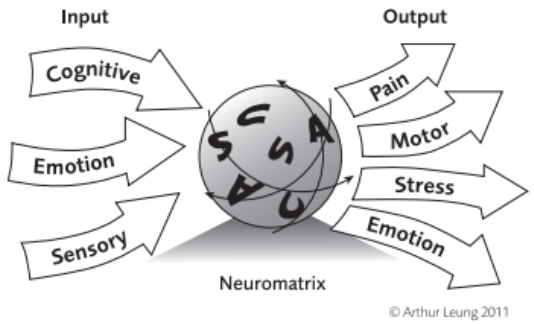


Figure 2. The concept of the neuromatrix theory for pain



Itself visualised as an entity (like an incessant spinning sphere) comprising the somatosensory (S), cognitive (C) and affective (A) domains, it receives inputs from areas of the brain governing sensation, emotions and cognitions and, in return, churns out a neurosignature (output) which activates various programmes for pain recognition, motor response, emotional and stress reactions. (Adapted from Melzack, Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004. Pain Pract. 2005 Jun;5(2):85–94.)

What is pain?

Subjective sensation	• with physical and psychological effects
Individual response	• dependant upon • age / gender / experience / personality / anxiety • settings / trust in clinician / fatigue
Organic and or psychological cause	
Measure	• Black line 10cm long? • questionnaires to assess disability • physical / mental

HOW DO WE FEEL THE "OUCH“?

Pain Process

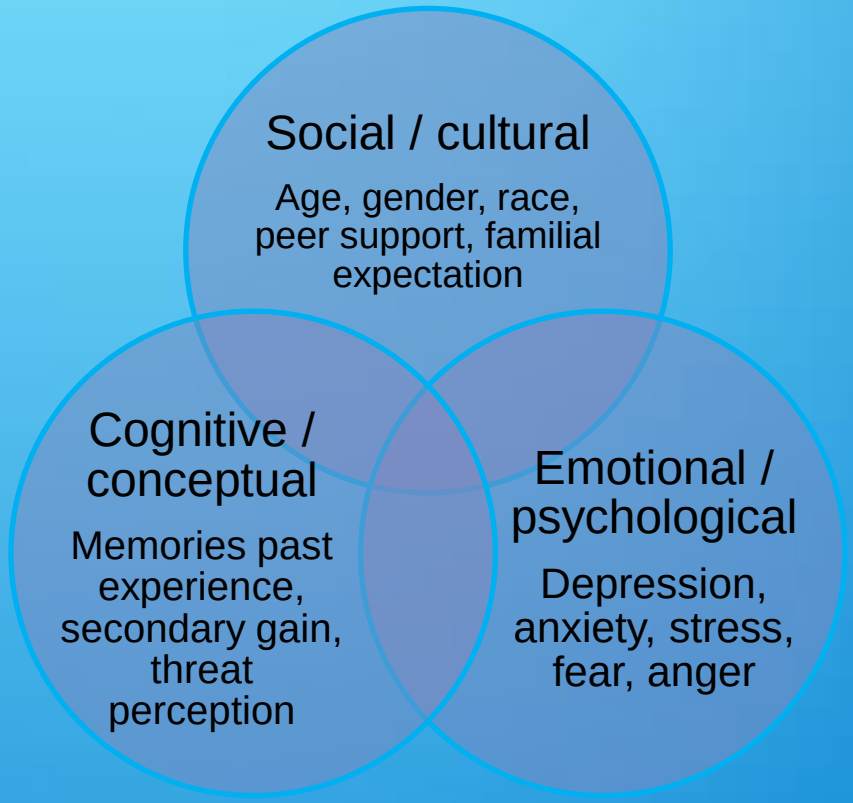
Nociception

Sensation

Behaviour

Suffering

Bio psycho social Model



NOCICEPTION-

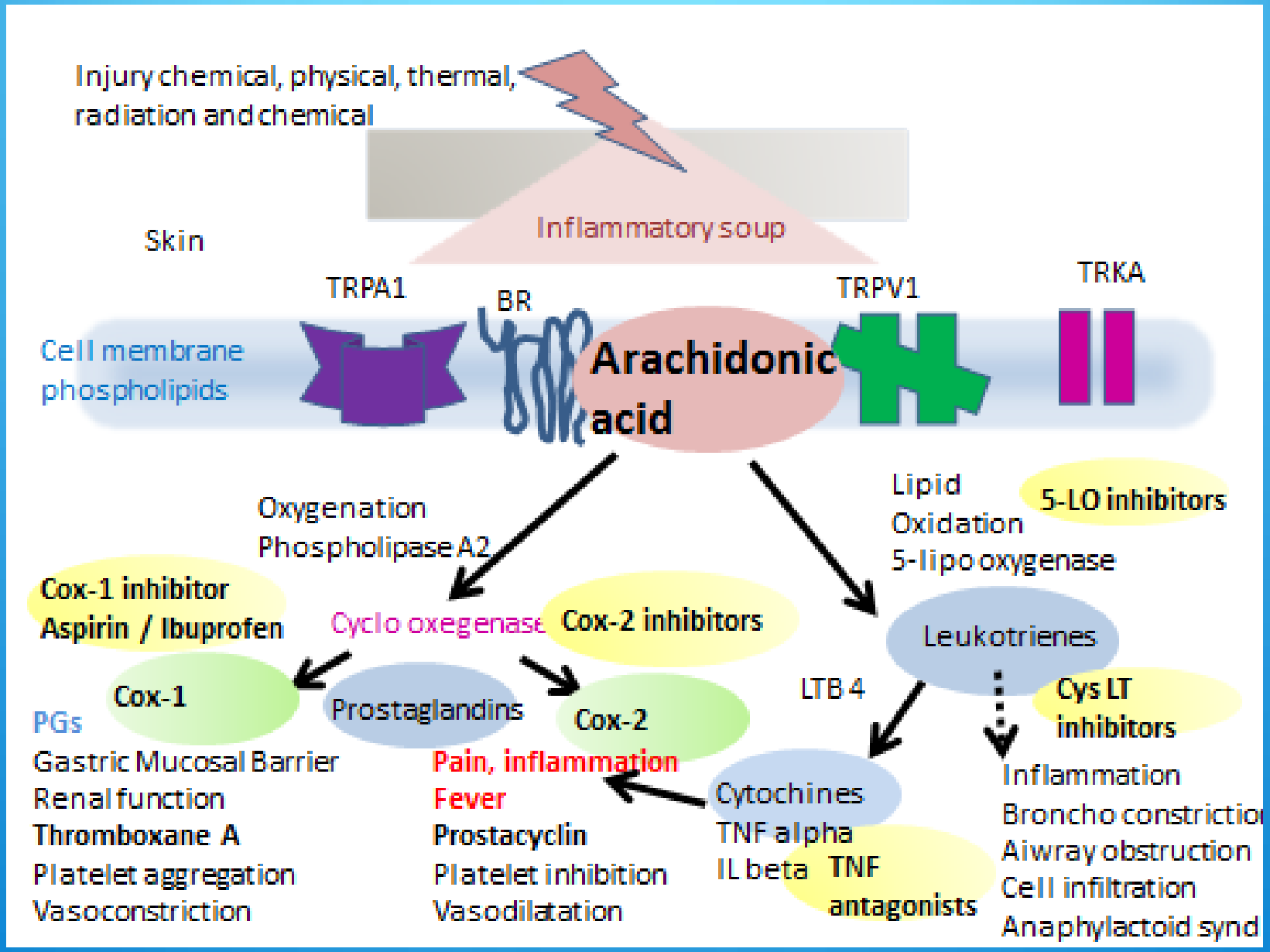
Inflammation
action potential
neural propagation of pain
ends sensory cortex

Nociception

- Tissue damage
- Chemical and electrical events
- Activation of the sensory cortex
- Pain recognition

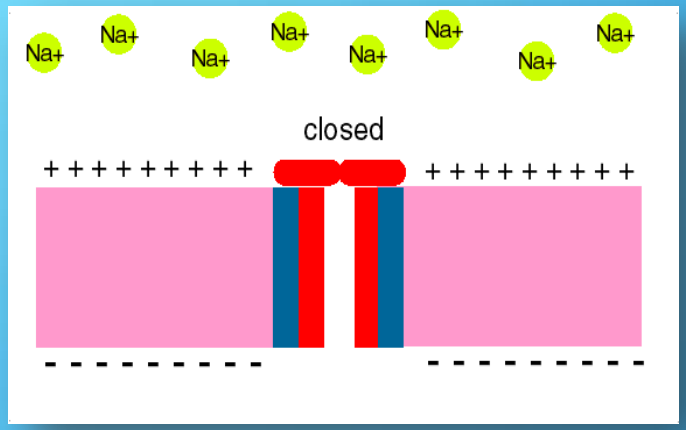
Nociception

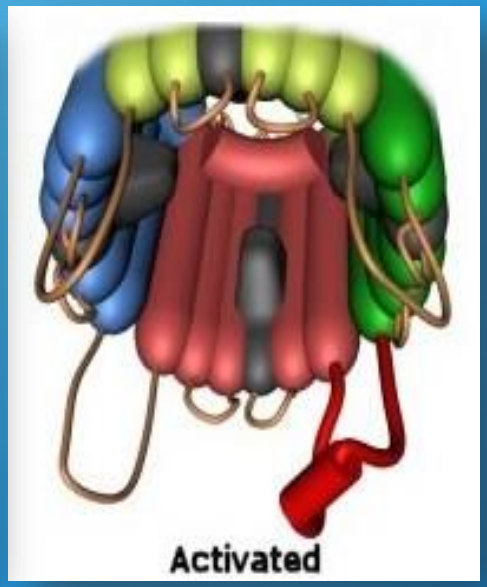
Peripheral events


Injury chemical, physical, thermal, radiation and chemical
Skin
Inflammatory soup
TRPA1
BR
TRPV1
TRKA
Cell membrane phospholipids
Arachidonic acid
Oxygenation
Phospholipase A2
Lipid Oxidation
5-lipo oxygenase
5-LO inhibitors
Cox-1 inhibitor
Aspirin / Ibuprofen
Cyclo oxegenase
Cox-2 inhibitors
Leukotrienes
Cox-1
Prostaglandins
Cox-2
LTB 4
Cys LT inhibitors
PGs
Gastric Mucosal Barrier
Renal function
Thromboxane A
Platelet aggregation
Vasoconstriction
Pain, inflammation
Fever
Prostacyclin
Platelet inhibition
Vasodilatation
Cytochines
TNF alpha
IL beta
TNF antagonists
Inflammation
Broncho constriction
Aiwray obstruction
Cell infiltration
Anaphylactoid synd

Specific pain receptors

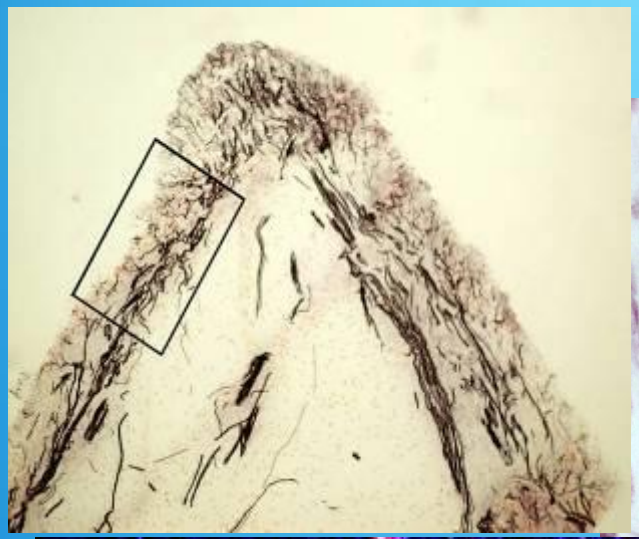
- Transmitters
  ↓NGF, ↓ SP, ↓ CGRP
- Receptors
  ↓ TRPV1, ↓ P2X3
- Ion Channels
  - Na, Ca, K
- Anatomy
  - degeneration
- ↑ spontaneous activity

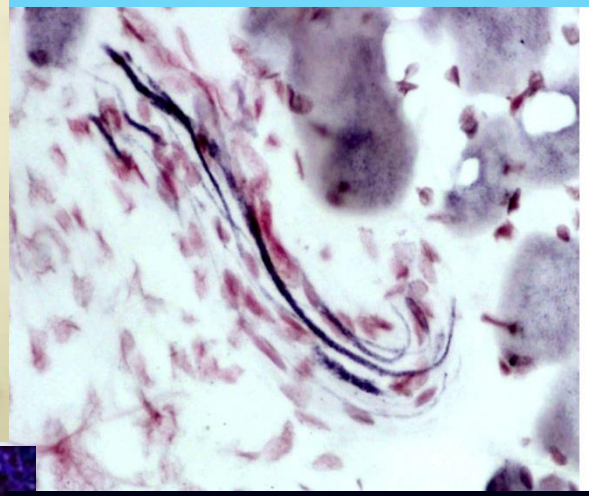


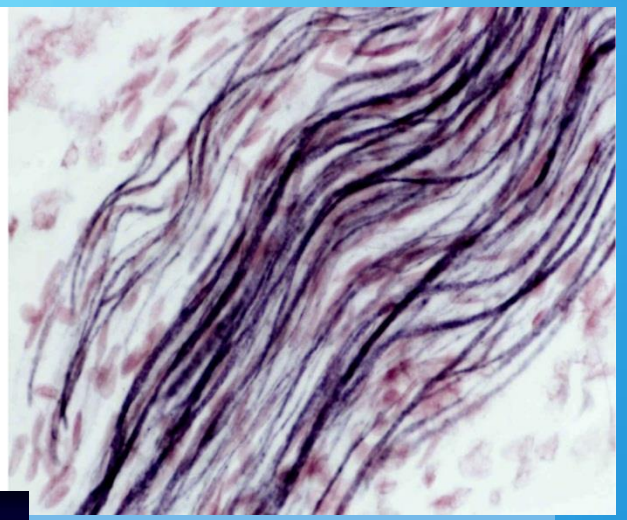


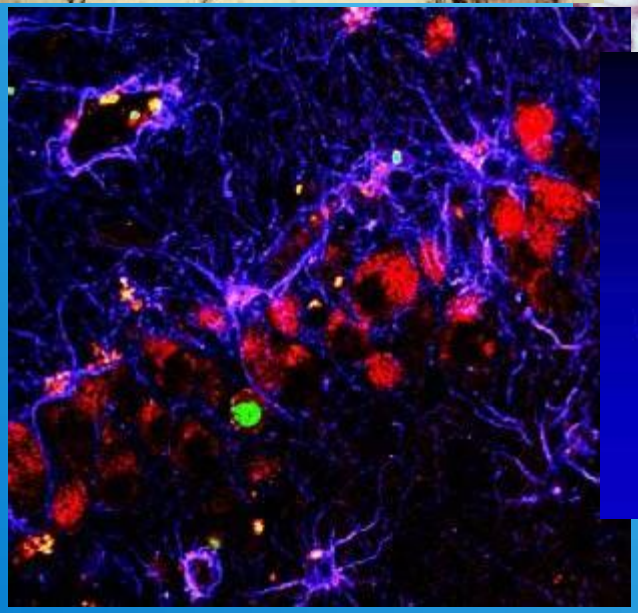
Control

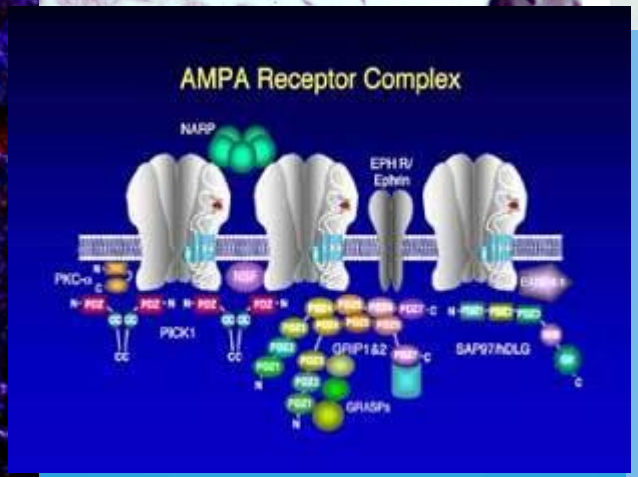
Pain

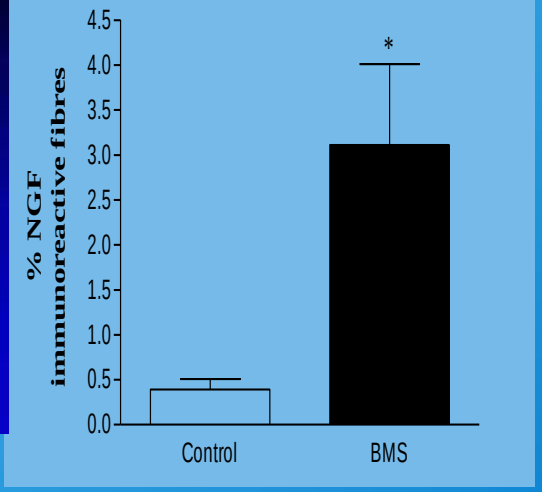






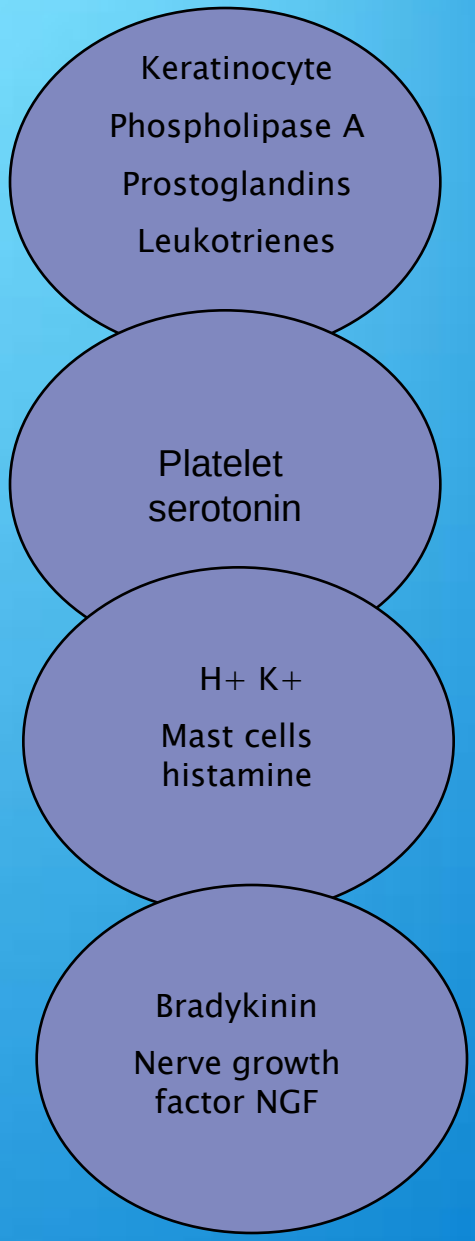






Peripheral Acute inflammatory pain

- Tissue injury
- Cell damage
  - Trauma mechanical, chemical . Radiation. heat
- Cytokine release
  - Attract immune cells
  - Nerve activation via receptors via NGF
- Neural depolarisation (PNS)
  - Action potential
  - Signals primary, secondary, tertiary (CNS)
  - Cortical activation 'sensing
  - Reaction (motor and sensory
- More cytokine release NEUROINFLAMMATION
- If process prolonged = changes in nervous system
- Chronic non inflammatory pain



Nociception central events

CNS and PNS

Receptor

Primary sensory nerve

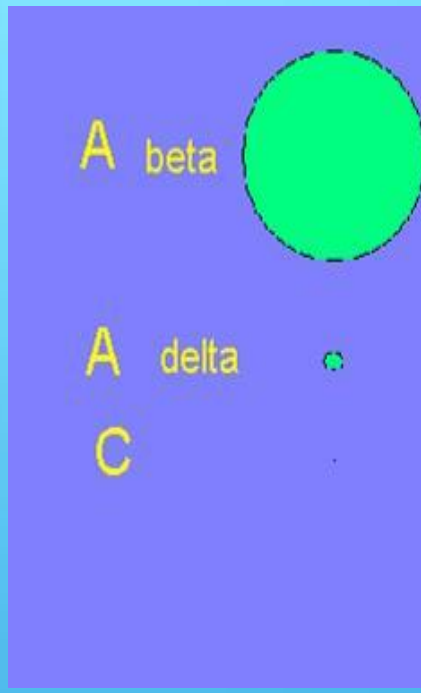
- A Delta and C fibres

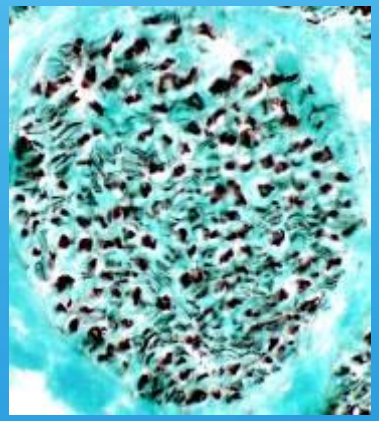
Secondary sensory nerve

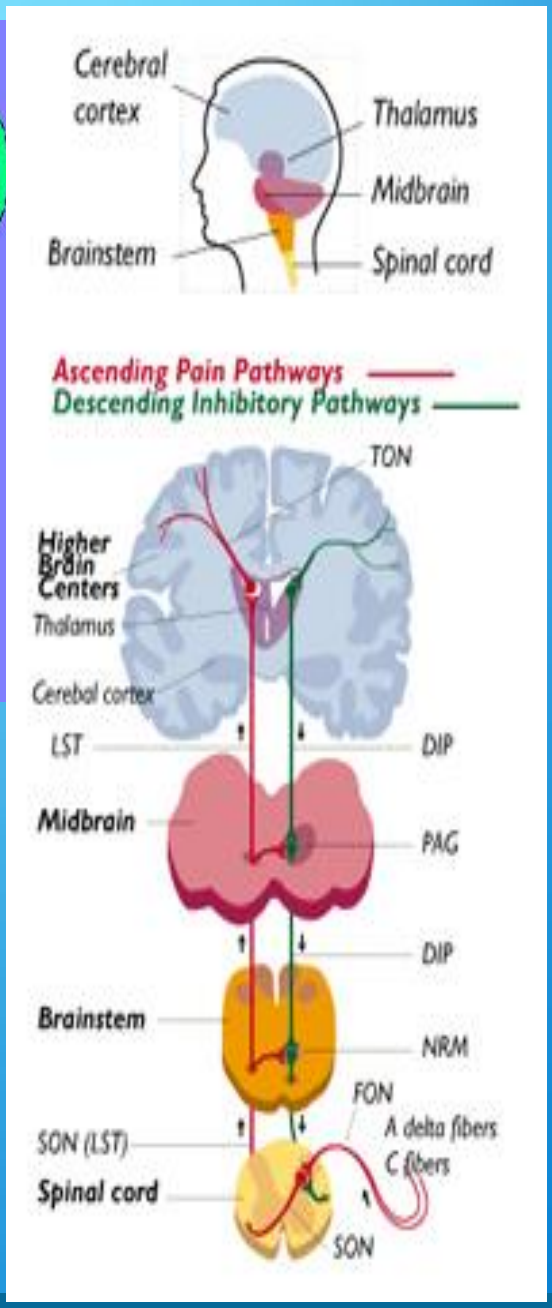
- Lamina I DRG

Tertiary sensory nerve

- Specific areas of the brain
  - Thalamus
  - Anterior cingulate cortex
  - S1 / S2
  - Insula
  - Brainstem







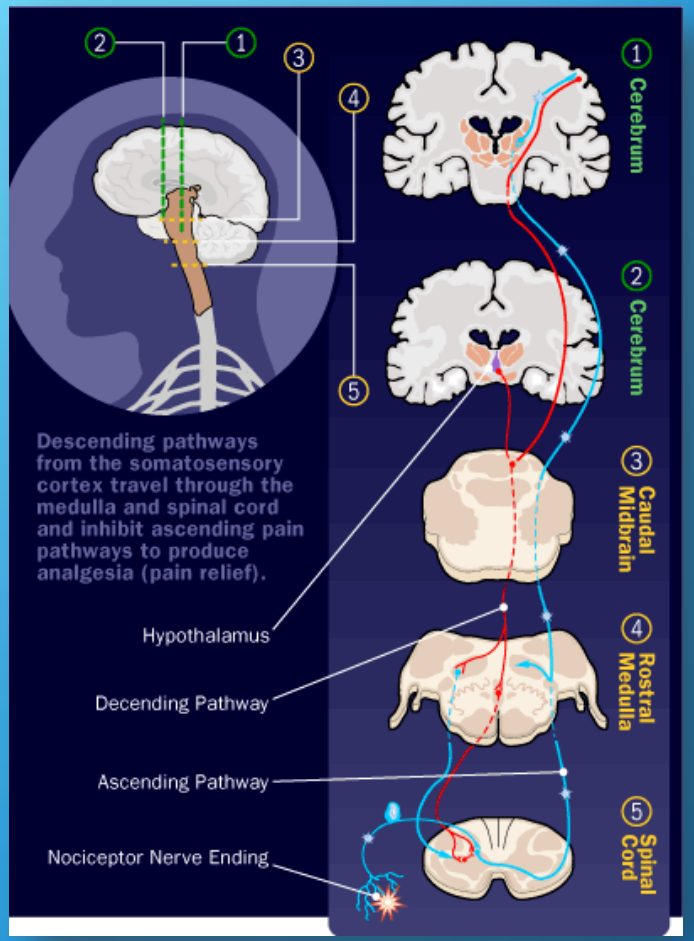
Noxious stimulus
What events unfold in the **sensory** system?

Neurophysiological

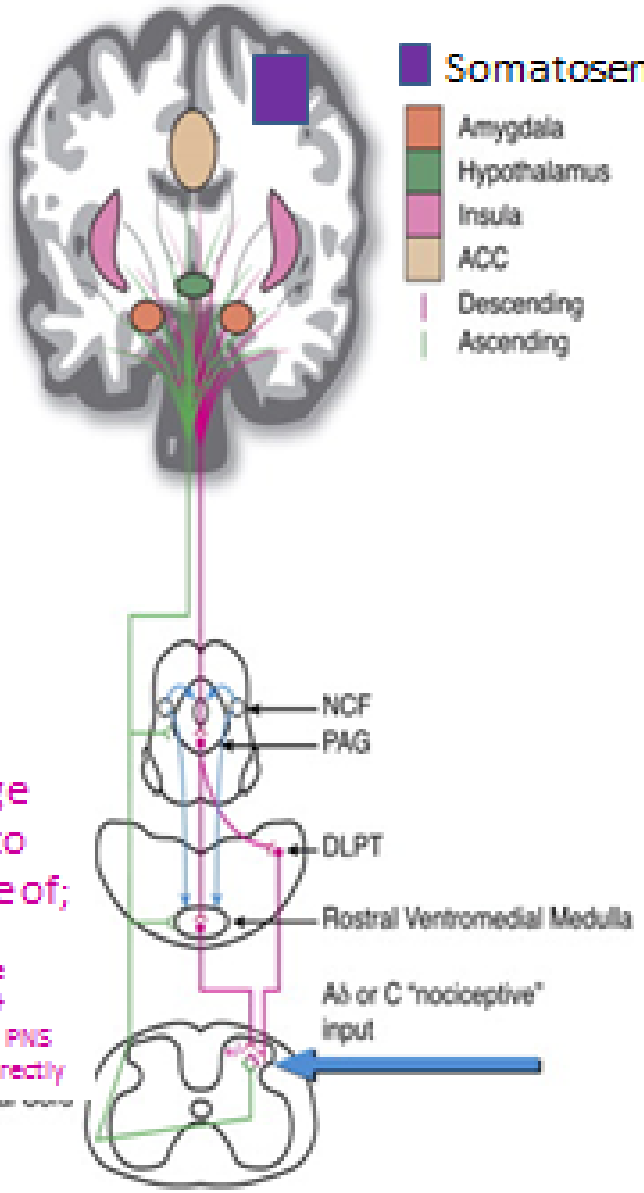
- Peripheral nervous system PNS
  - Inflammation
  - Receptors
  - Axons (primary / secondary / tertiary [cortex])
  - neurotransmission
- Central nervous system CNS
  - Pain pathways

Patient

- Clinical symptoms
- Psychological factors
- Environmental factors
- **Reaction is Emotional and Physical**



Neuro inflammation



Tissue damage leads to release of;

ATP

Adrenaline

Protons H+

Activating PNS neurons directly

Cellular events

Astrocytes

Microglia

- (Macrophages invading the CNS)

Schwann cell

Macrophages

- Bradykinin
- IL*B*
- Nerve growth factor (NGF)

Mast cell

- Histamine
- 5HT
- PGE2
- Platelet activation factor (PAF)

Lymphocytes/Neutrophils

- IL*B*
- Endorphins acting on -CRK, GABA*α*, *SSTR2a*, *M3*

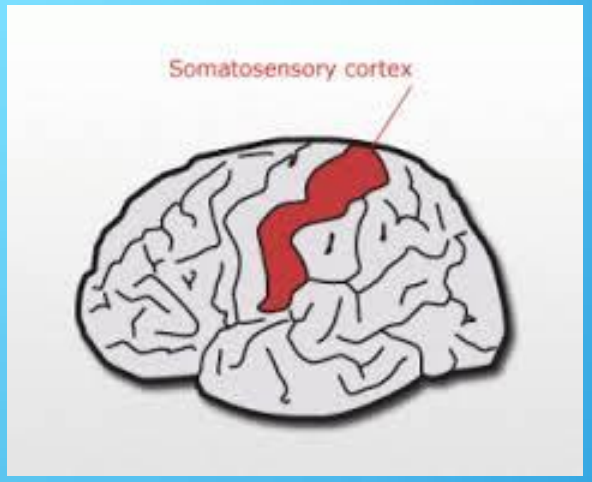
Neuroinflammatory

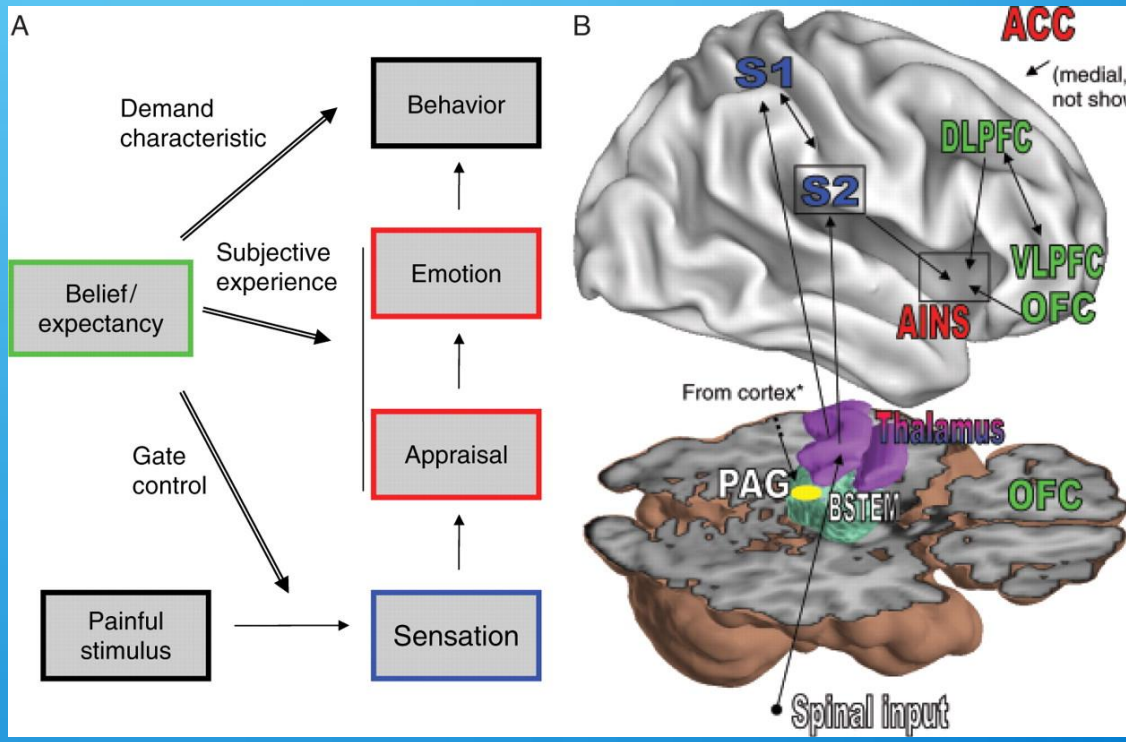
- Central centres
- Spinal cord
  - Receptor
    - CCR2
    - CCR1
    - CCR5
    - Cx3-CR1
  - Ligands
    - CCL2 (MCP-1)
    - CCL3 (MIP-1α)
    - CX3CL1 Fractalkaline
- Dorsal root ganglion
  - Receptors
    - CX3CR-1
    - CCR5
    - CXCR4
  - Ligands
    - CCL2 (MCP-1)
    - CCL21 (SLC)
    - CX3CL1 Fractalkaline
- Peripheral nerve
  - Receptors
    - Heat, acid TRPV1
    - TTXR Nav
    - 5HT
    - H1
    - IL 1 and 6
    - TrkA
    - P2X3
    - A5
    - ASIC
    - glutamate
  - Ligands
    - CCL2 (MCP-1)
    - CCL3 (MIP-1α)
    - CX3CL1 Fractalkaline

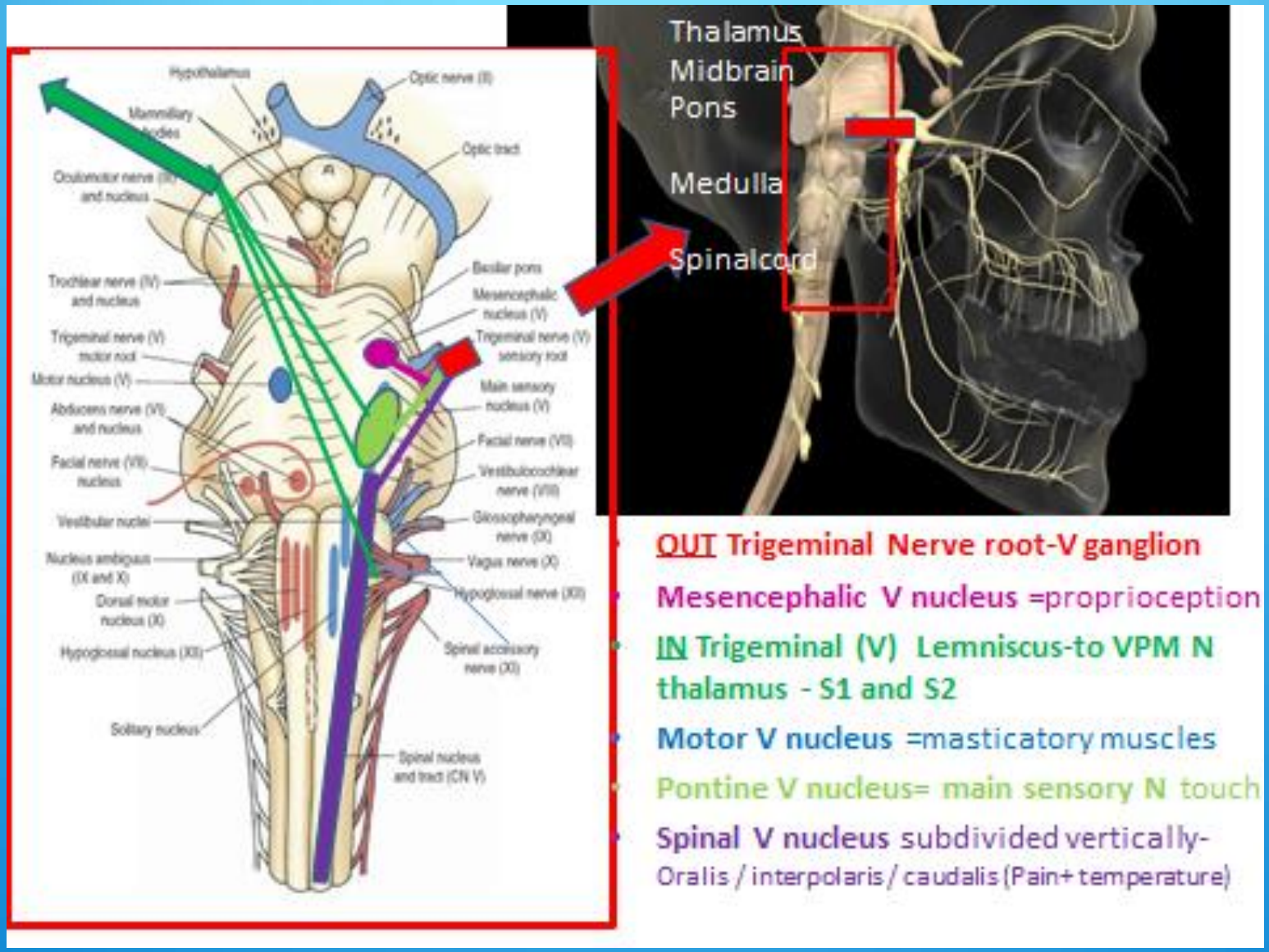
SENSATION

Central neuroanatomy

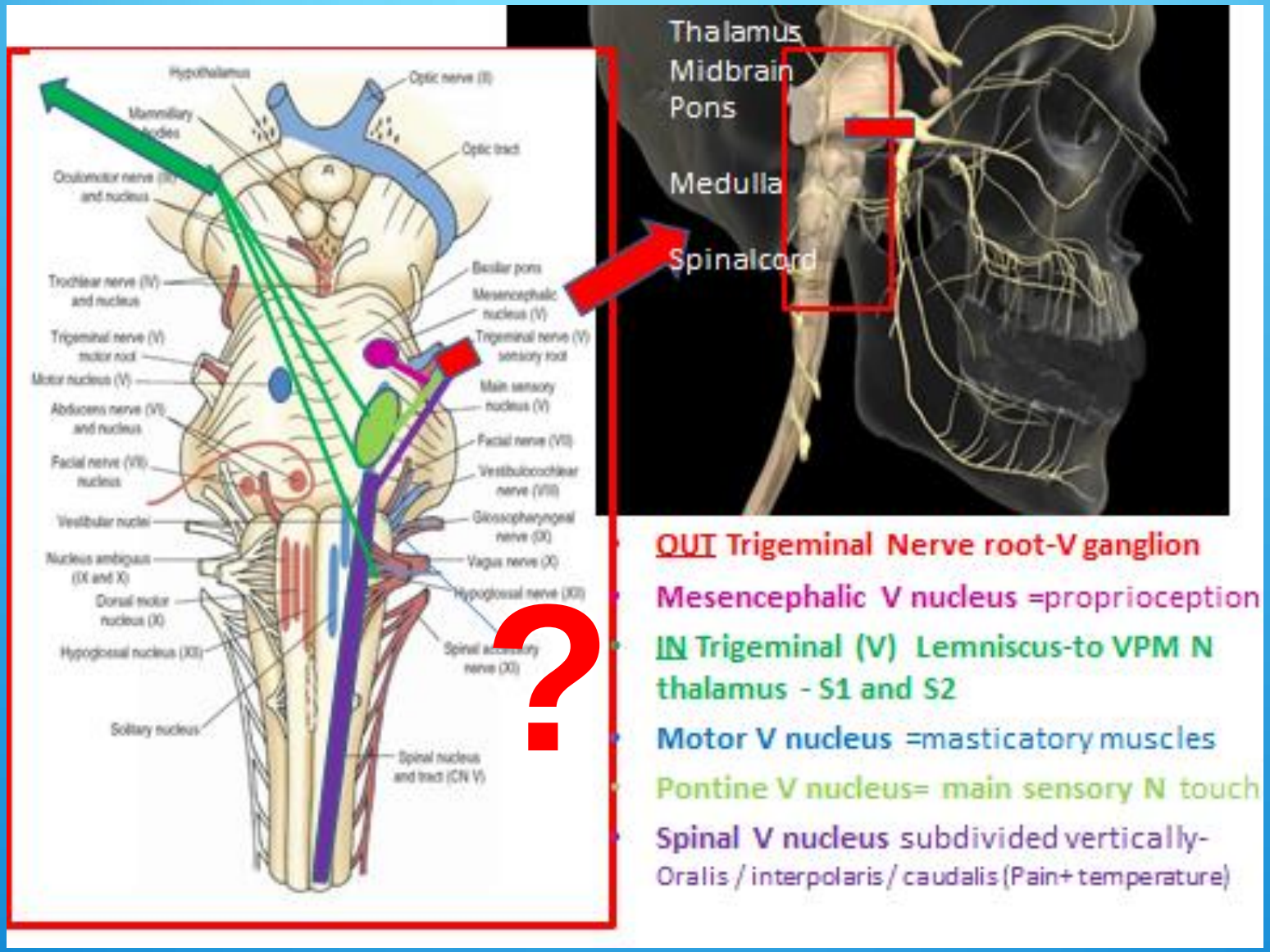
- Pain related areas
  - **Spinal cord C1-S5**
    - C1-8/T1-12/L1-5/S1-5
    - distal root ganglion
      - Ventral horn = motor
      - Dorsal horn = sensory
- Specific areas of the brain
  - Brainstem
    - Cranial nerve
    - Thalamus
    - Hypothalamus
    - Cerebellum
  - Forebrain
    - Cortex-sensation
      - Anterior cingulate cortex
      - S1 and S2
    - Limbic system -memory
    - Basal ganglia-movement







- OUT Trigeminal Nerve root-V ganglion
- Mesencephalic V nucleus =proprioception
- IN Trigeminal (V) Lemniscus-to VPM N thalamus - S1 and S2
- Motor V nucleus =masticatory muscles
- Pontine V nucleus= main sensory N touch
- Spinal V nucleus subdivided vertically- Oralis / interpolaris / caudalis (Pain+ temperature)


Thalamus
Midbrain
Pons
Medulla
Spinalcord
Hypothalamus
Optic nerve (II)
Mammillary bodies
Optic tract
Oculomotor nerve (III) and nucleus
Trochlear nerve (IV) and nucleus
Basilar pons
Mesencephalic nucleus (V)
Trigeminal nerve (V) motor root
Trigeminal nerve (V) sensory root
Motor nucleus (V)
Main sensory nucleus (V)
Abducens nerve (VI) and nucleus
Facial nerve (VII)
Facial nerve (VII) nucleus
Vestibulocochlear nerve (VIII)
Vestibular nuclei
Glossopharyngeal nerve (IX)
Nucleus ambiguus (IX and X)
Vagus nerve (X)
Dorsal motor nucleus (X)
Hypoglossal nerve (XII)
Hypoglossal nucleus (XII)
Spinal accessory nerve (XI)
Solitary nucleus
Spinal nucleus and tract (CN V)
?
OUT Trigeminal Nerve root-V ganglion
Mesencephalic V nucleus =proprioception
IN Trigeminal (V) Lemniscus-to VPM N thalamus - S1 and S2
Motor V nucleus =masticatory muscles
Pontine V nucleus= main sensory N touch
Spinal V nucleus subdivided vertically-
Oralis / interpolaris / caudalis (Pain+ temperature)

Anatomy revisited Sensory cortex V

ACC

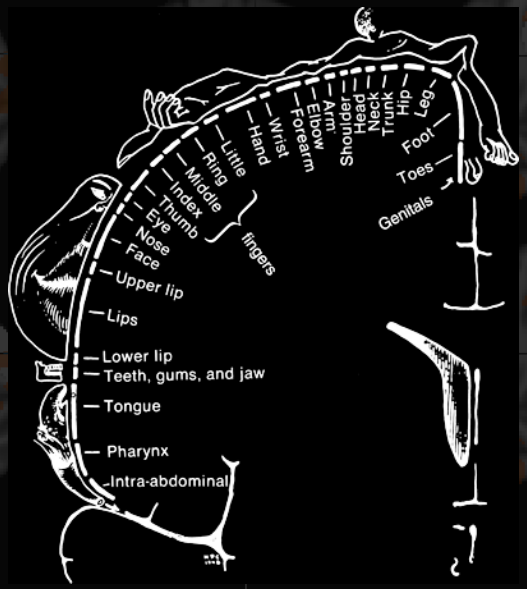
PCC

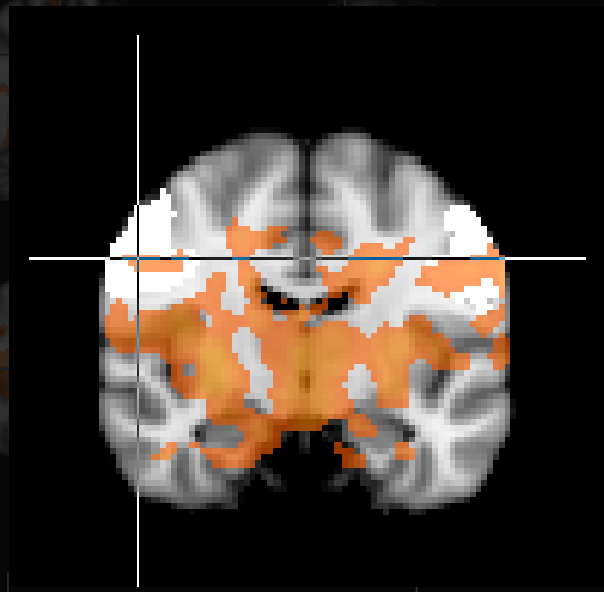
S1

S2

THAL

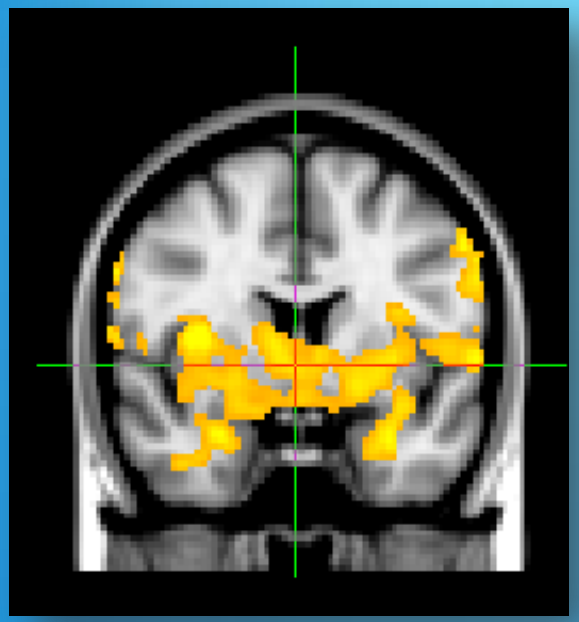
INS

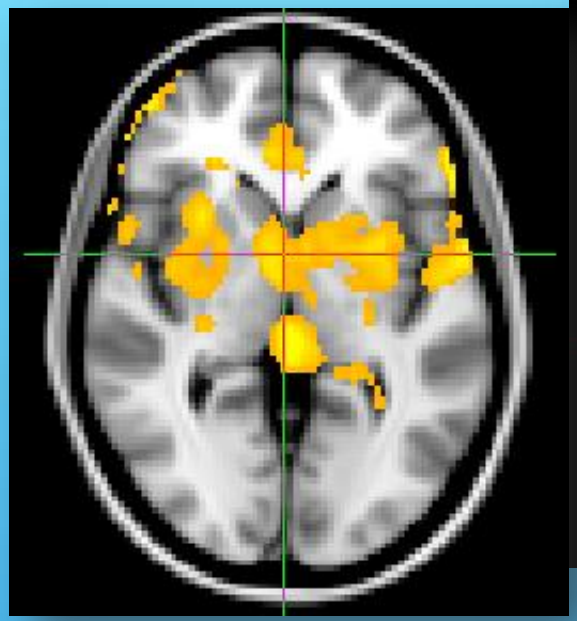


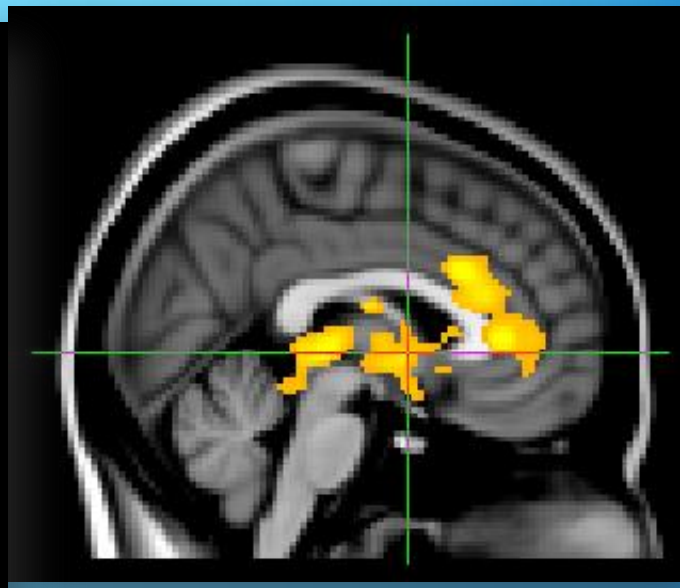


•Additional amygdala, hippocampus, brainstem, and V5 ROIs

Main effect of TME pain, right tooth, cluster corrected α <0.05

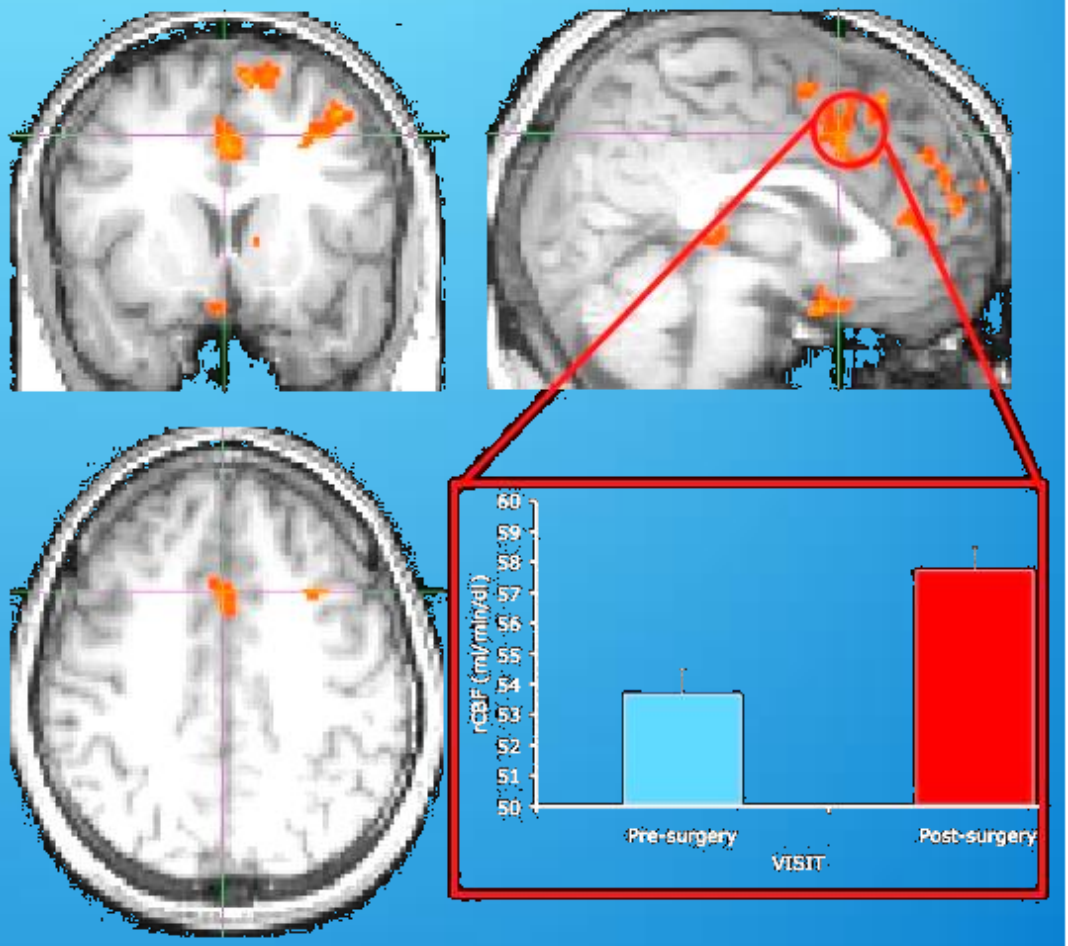






Central pain activity

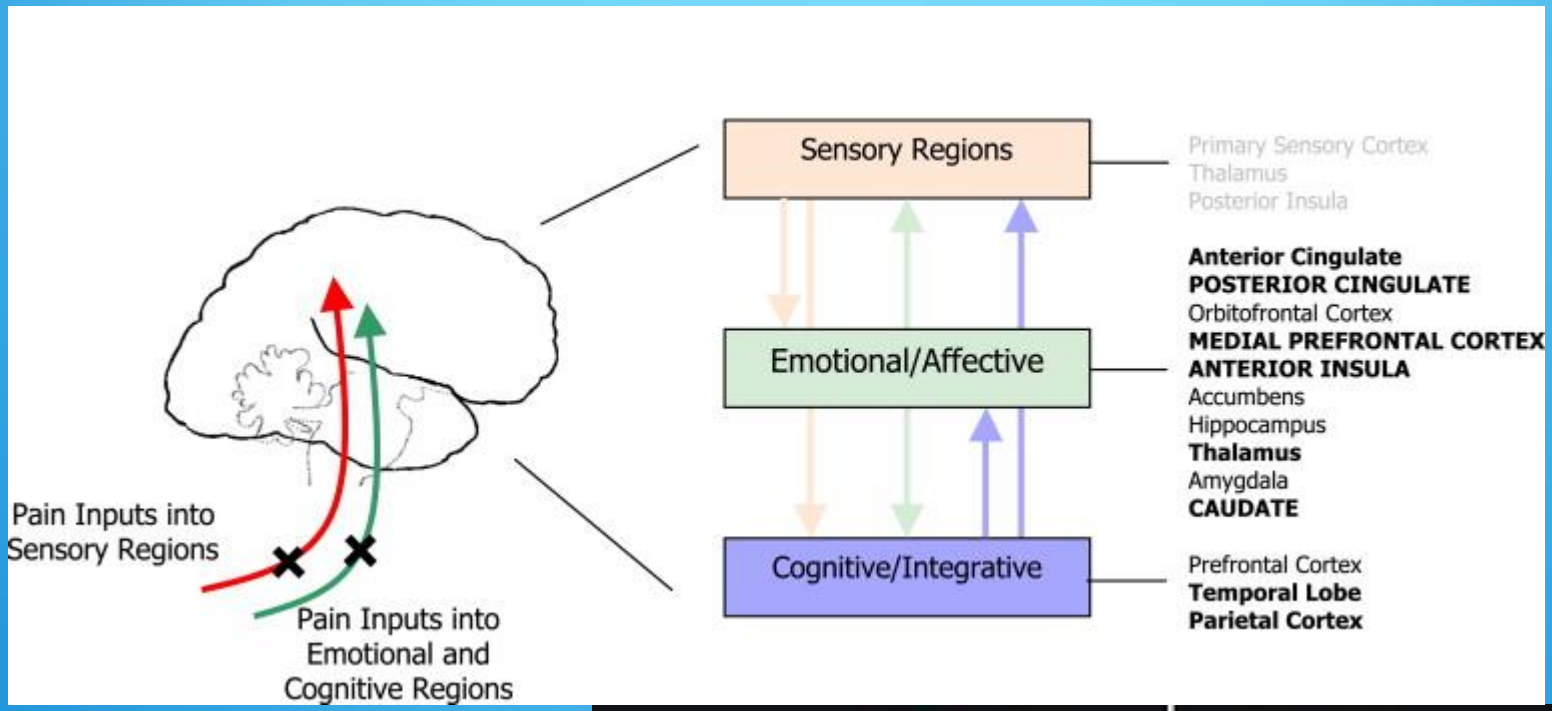
- Pain related areas
  - Spinal cord C1-S5
    - C1-8/T1-12/L1-5/S1-5
    - distal root ganglion
      - Ventral horn = motor
      - Dorsal horn = sensory
  - Brain stem
    - Cranial nerve
    - Thalamus
    - Hypothalamus
    - Cerebellum
  - Forebrain
    - Cortex-sensation
    - Limbic system -memory
    - Basal ganglia-movement

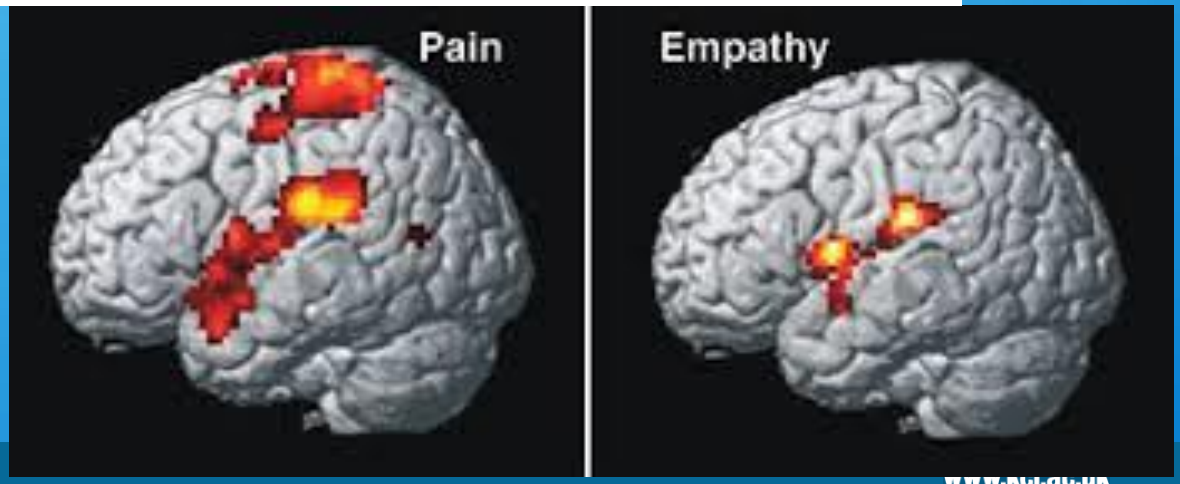


Behaviour

- History
- Stress
- Anxiety
- Culture
- Ethnicity
- Beliefs
- Age
- Environment
- Context

Affective emotional areas of Brain



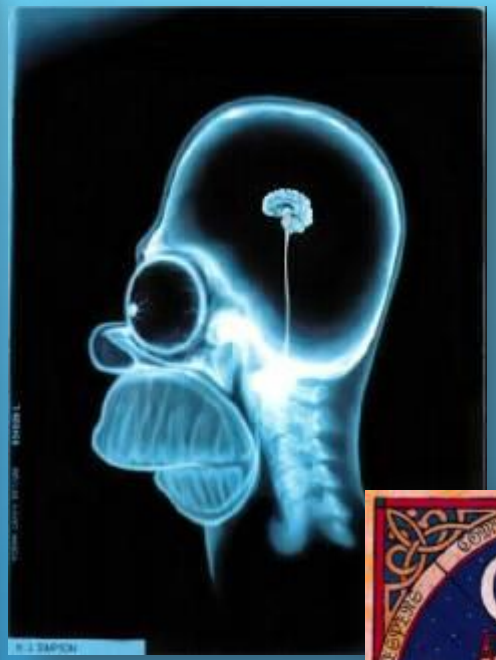


Perception of pain

Perception of pain

‘I enjoy the pain’

David Beckham on tattoos



Opus Dei Priest ‘Pain is good’

Suffering

History
Stress
Anxiety
Culture
Ethnicity
Beliefs
Age
Environment
Context

Personality
Religion
Placebo
Anger
Catastrophising
Fear

Catastrophising

Sullivan M et al. Perceived Injustice is Associated with Heightened Pain Behavior and Disability in Individuals with Whiplash Injuries. Psychol. Inj. and Law DOI 10.1007/s12207-009-9055-2

Anxiety stress and pain

Psychological factors driving pain

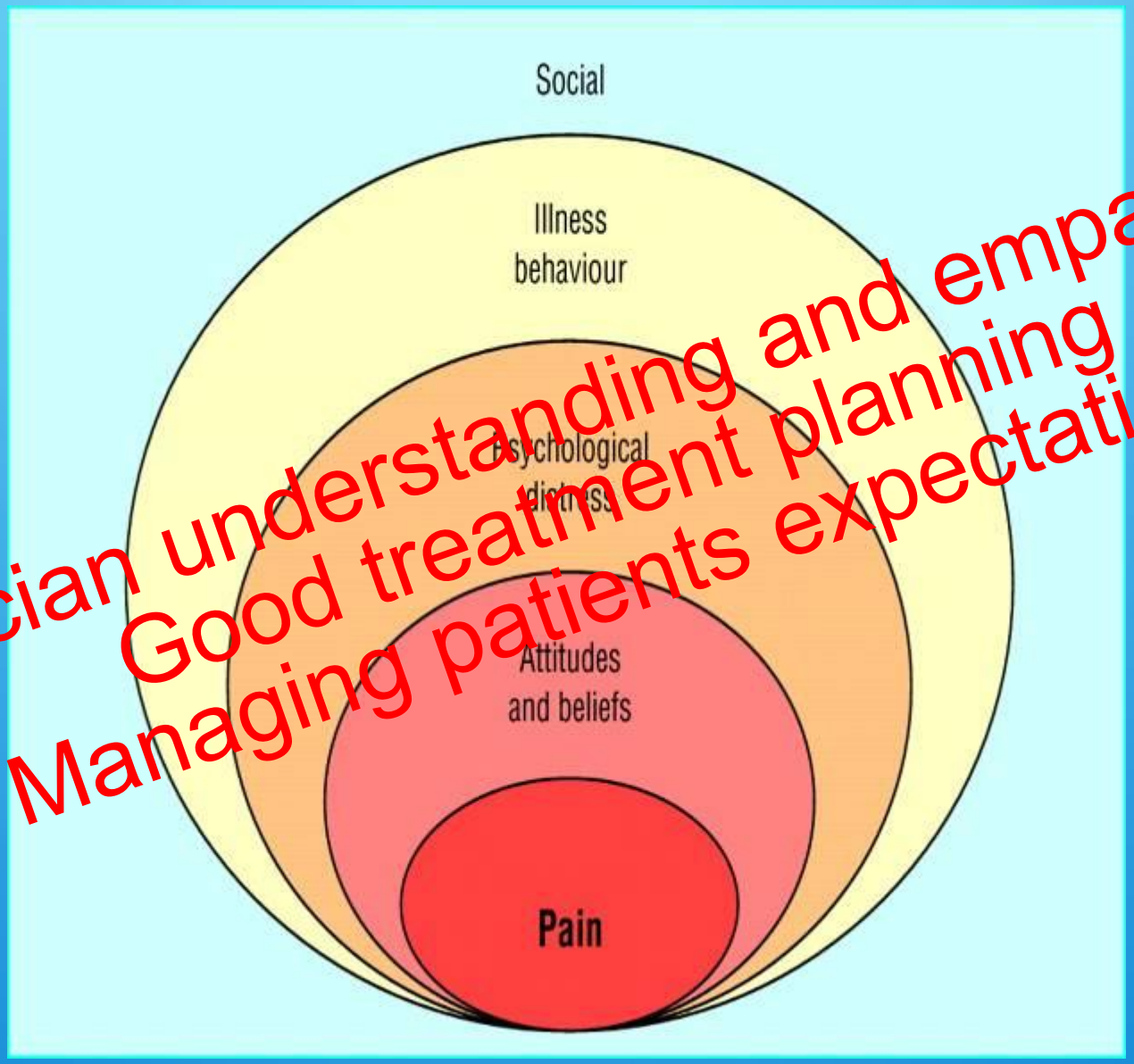
Sullivan MJ et al. Catastrophizing and perceived injustice: risk factors for the transition to chronicity after whiplash injury. Spine (Phila Pa 1976). 2011 Dec 1;36(25 Suppl):S244-9 Dec;92(12):2041-56. Review

Lajnert V, et al Depression, somatization and **anxiety** in female patients with temporomandibular disorders (TMD). Coll Antropol. 2010 Dec;34(4):1415-9

Alternative and holistic management of pain

Bauer B et al. Effect of the combination of music and nature sounds on **pain** and **anxiety** in cardiac surgical patients: a randomized study. Altern Ther Health Med. 2011 Jul-Aug;17(4):16-23.

Louw A, et al.The effect of neuroscience education on **pain**, disability, **anxiety**, and **stress** in chronic musculoskeletal **pain**. Arch Phys Med Rehabil. 2011



Clinician understanding and empathetic
Good treatment planning
Managing patients expectations

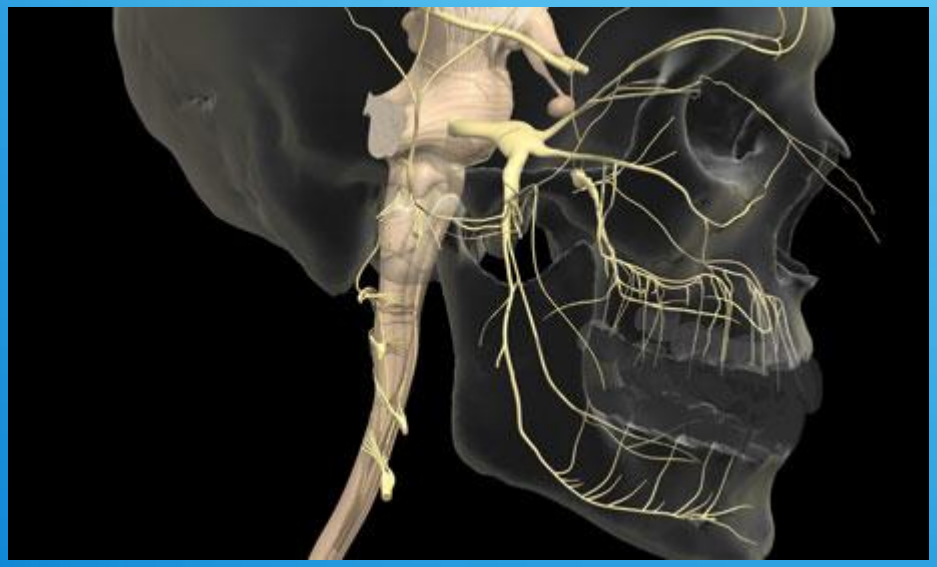
- Managing patients expectations of surgical related pain is effective in pain relief !

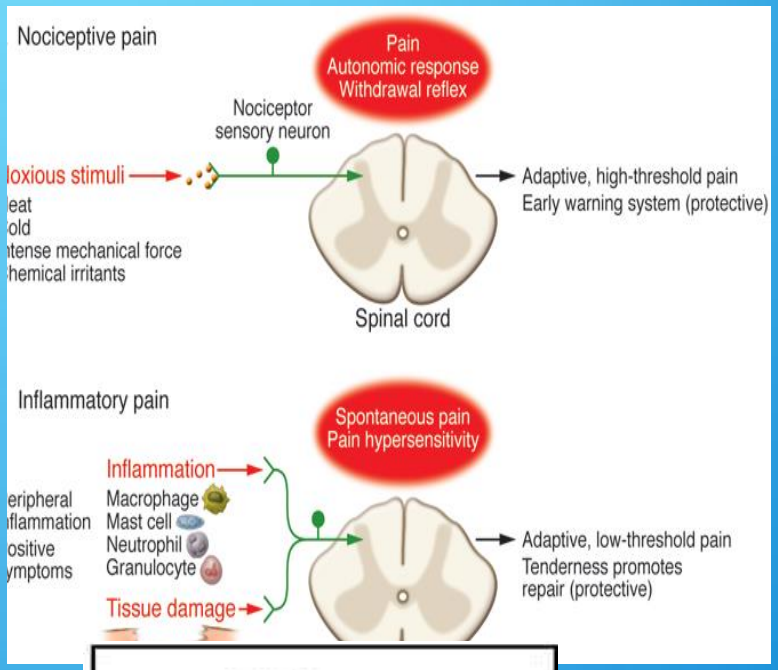
Relationship between preoperative expectations, satisfaction, and functional outcomes in patients undergoing lumbar and cervical spine surgery: a multicenter study. Soroceanu A, Ching A, Abdu W, McGuire K. Spine (Phila Pa 1976). 2012 Jan 15;37(2):E103-8

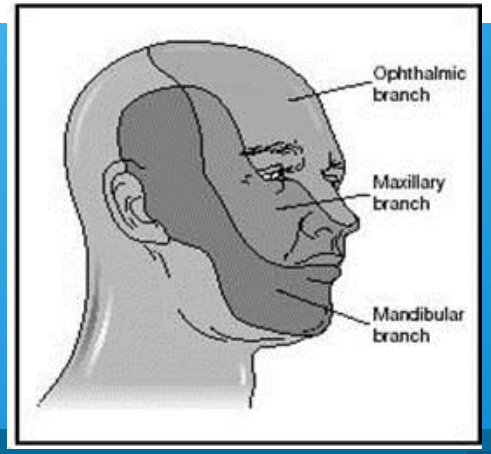
TYPES OF PAIN

Types of acute pain

- Nociceptive
- Inflammatory





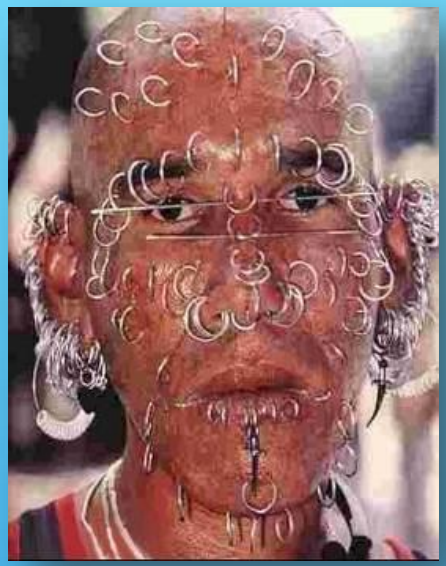


Pain: Acute

‘Healthy pain’ due to inflammation

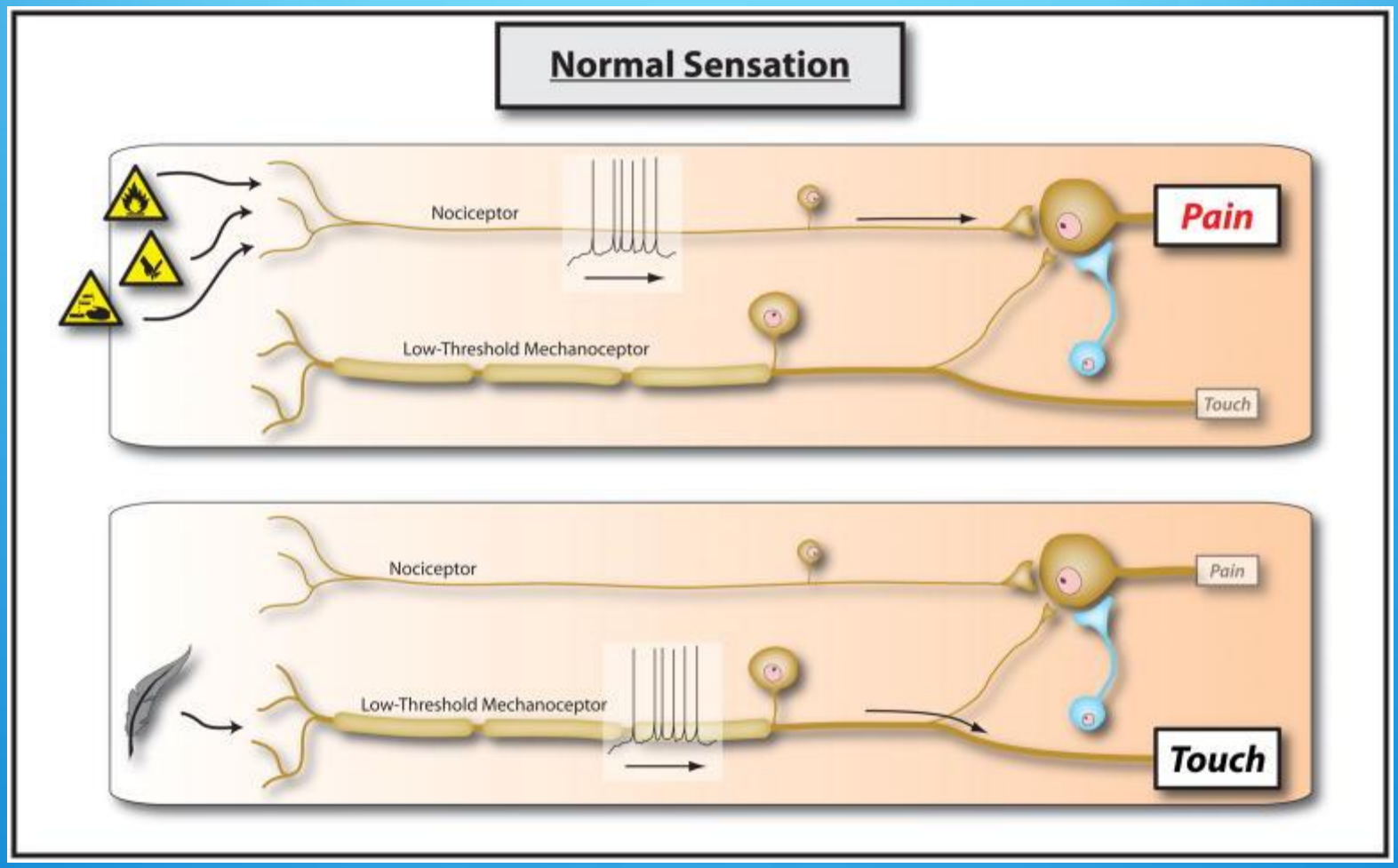
Infection / autoimmune / trauma

Thermal / mechanical / chemica

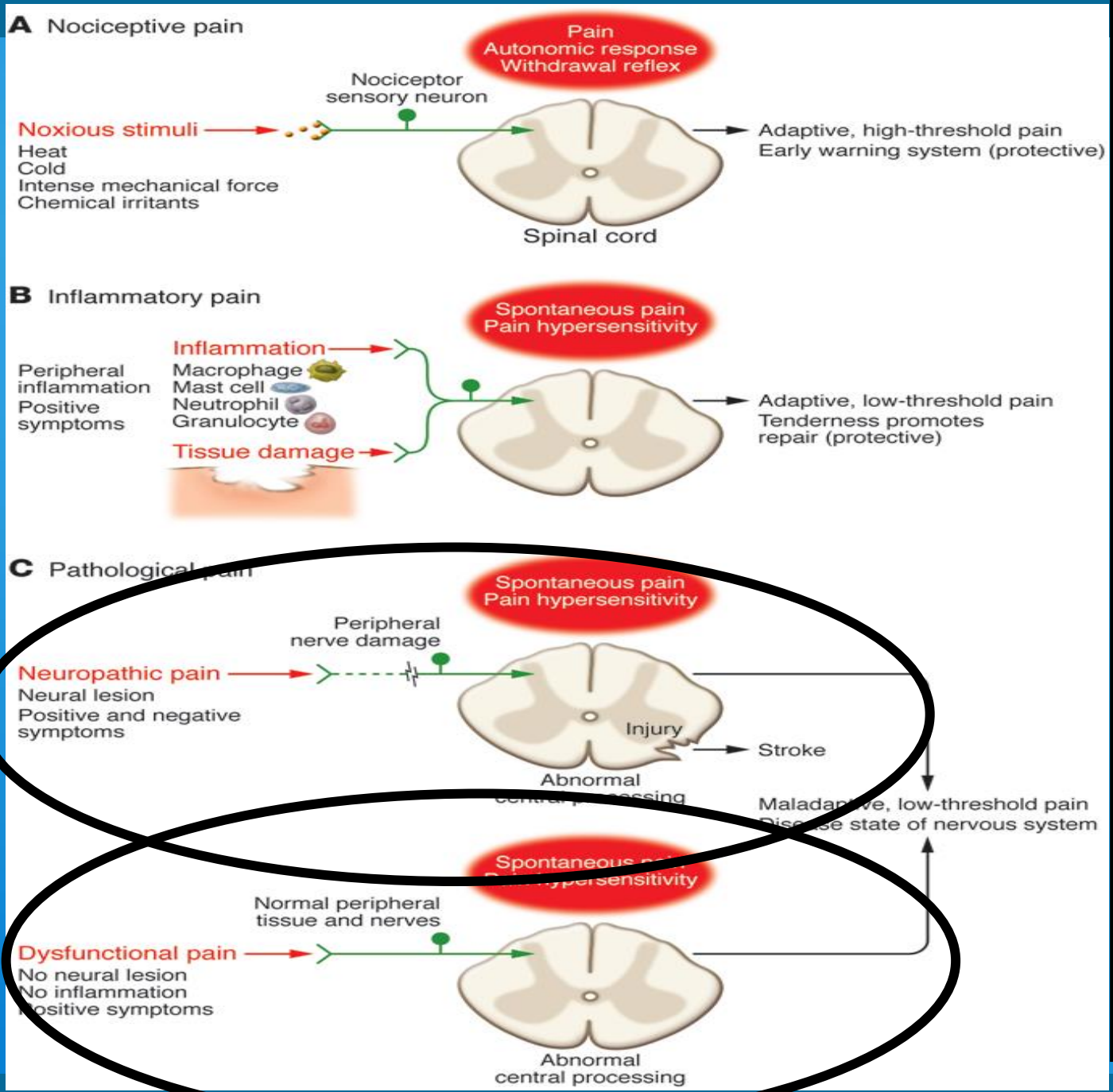


Why does the acute pain patient present?

- Infections
  - Odontogenic > dry socket > AHGS > ANUG > Sialadenitis > sinusitus > otitis media > septic arthritis> STDs
- Trauma
  - Post surgical (acute and chronic-nerve injury)
  - TMJ -/dislocation / Subluxation –open/closed locking
  - Dental or bone fractures
- Inflammatory –
  - TMJ pain = Temporomandibular dysfunction (TMD) = Arthromyalgia/Dysfunction/ Arthritides
  - Mucosal lesions Aphthous ulceration, Vesiculo bullous disorders
  - Autoimmune disorders


Normal Sensation
Nociceptor
Pain
Low-Threshold Mechanoceptor
Touch
Nociceptor
Pain
Low-Threshold Mechanoceptor
Touch

- Chronic pain
  - NEUROPATHIC
  - DYSFUNCTIONAL

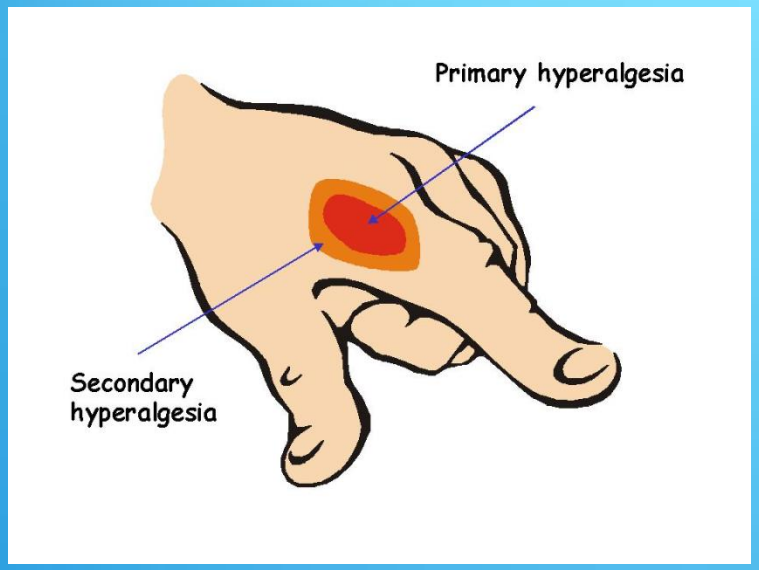


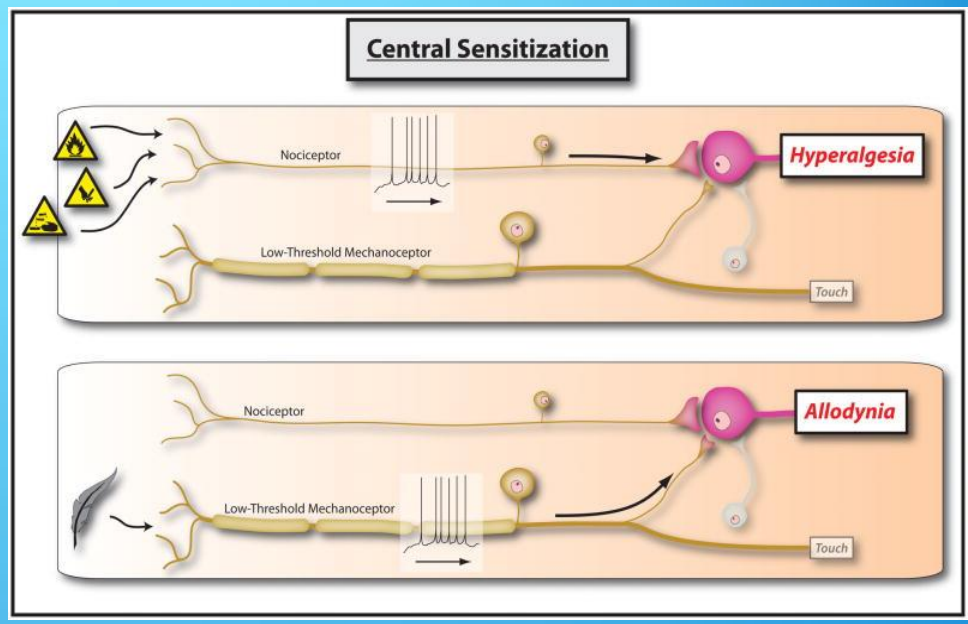
A Nociceptive pain
Pain caused by an non inflammatory response to a noxious stimulus =Tissue damage

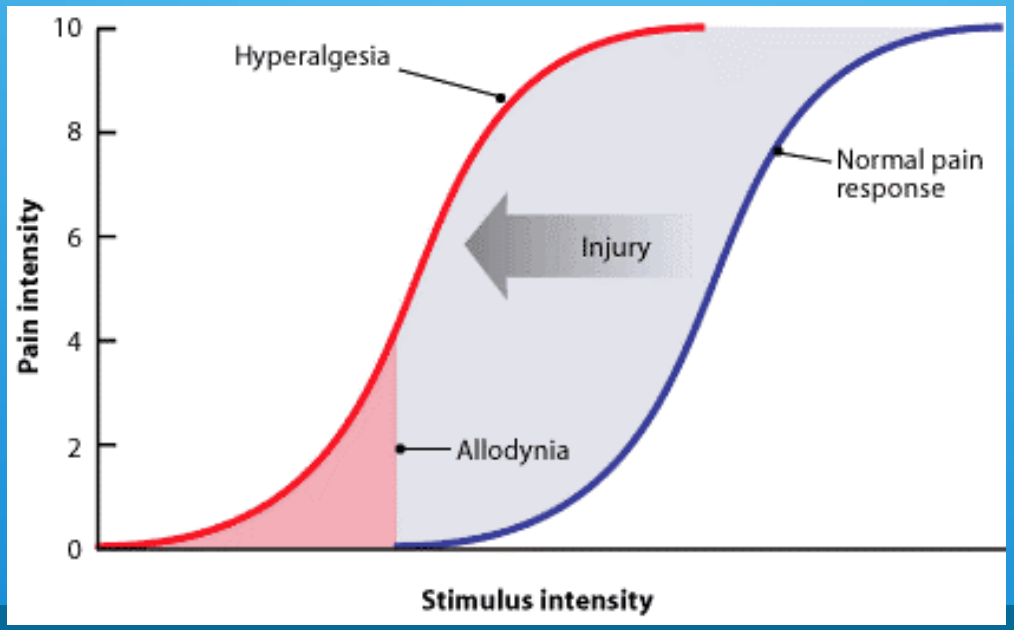
B Inflammatory pain

C Pathological pain
Neuropathic pain
Pain initiated or caused by a primary lesion or disease in the PNS or CNS = nerve damage

D Dysfunctional pain
REMEMBER it may be possible to have coincident combinations of A , B and or C types of pain


Primary hyperalgesia
Secondary hyperalgesia


Central Sensitization
Nociceptor
Hyperalgesia
Low-Threshold Mechanoceptor
Touch
Nociceptor
Allodynia
Low-Threshold Mechanoceptor
Touch


10
8
6
4
2
0
Pain intensity
Hyperalgesia
Normal pain response
Injury
Allodynia
Stimulus intensity

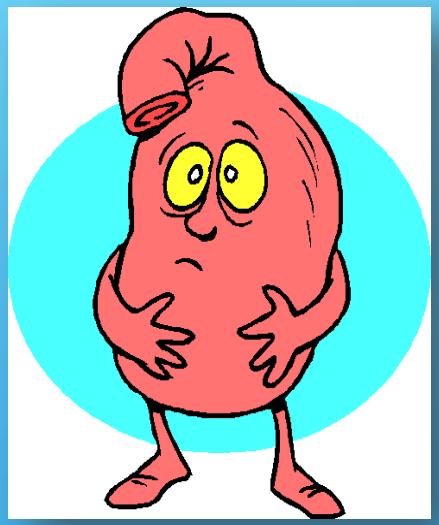
Chronic Pain

Unhealthy / Neuropathic pain lasting > 3 months

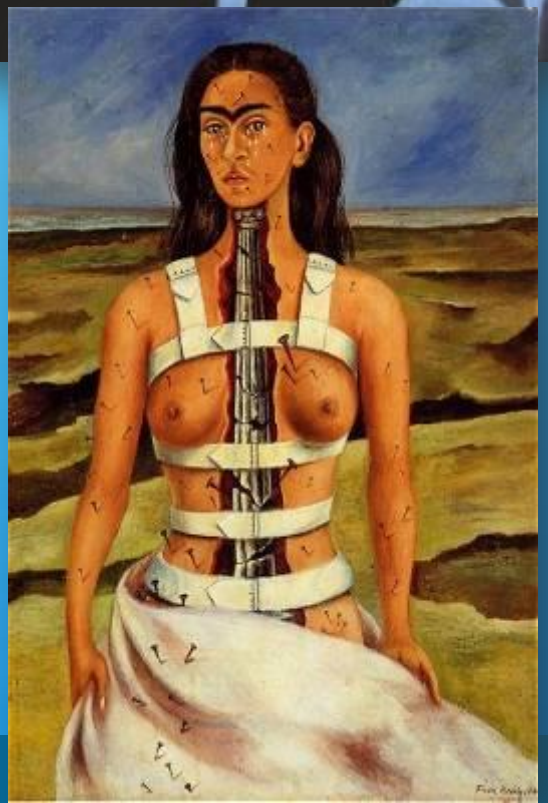
Back pain 47.5%

Head ache 45.2%

Joints 41.7%



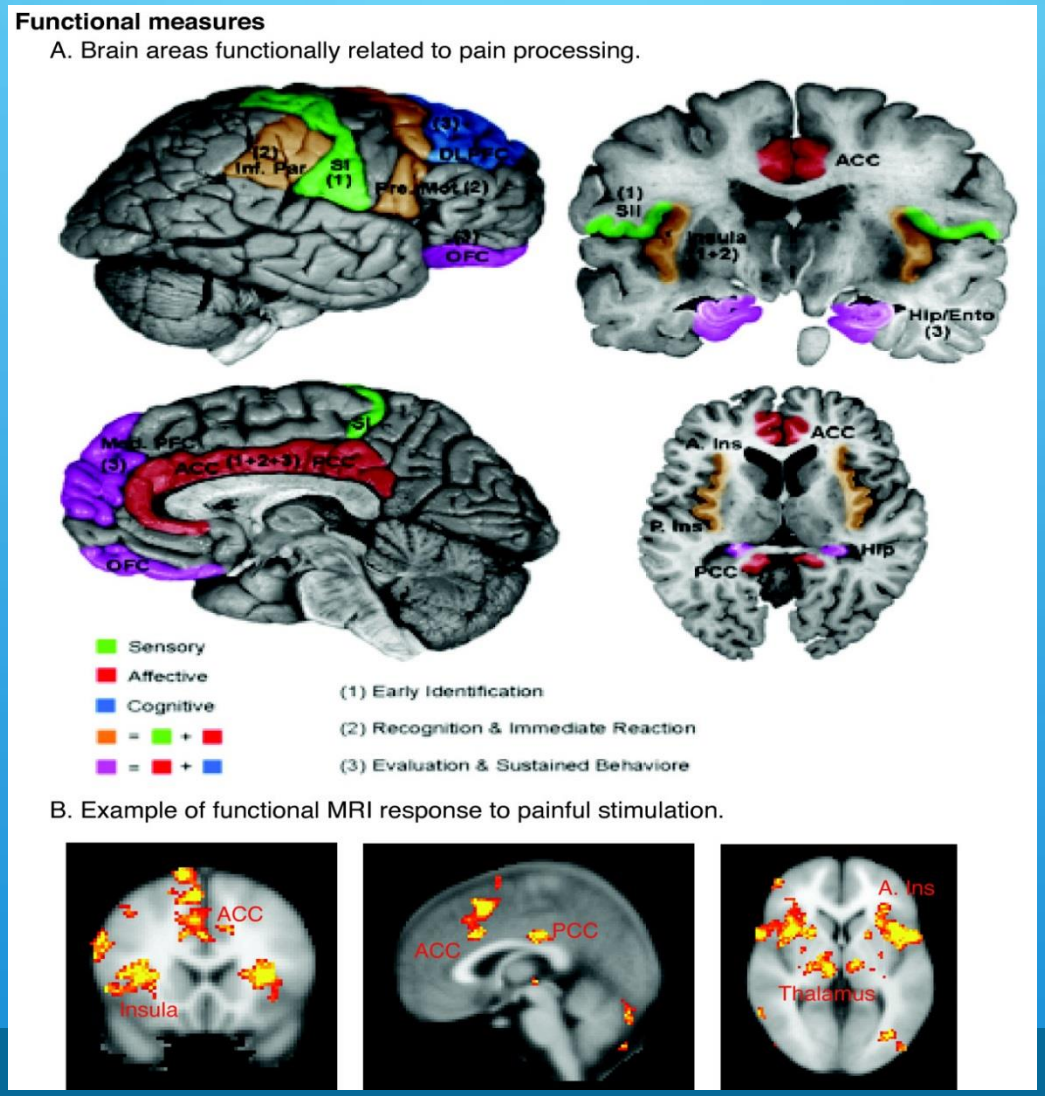
Disease of the neuromatrix

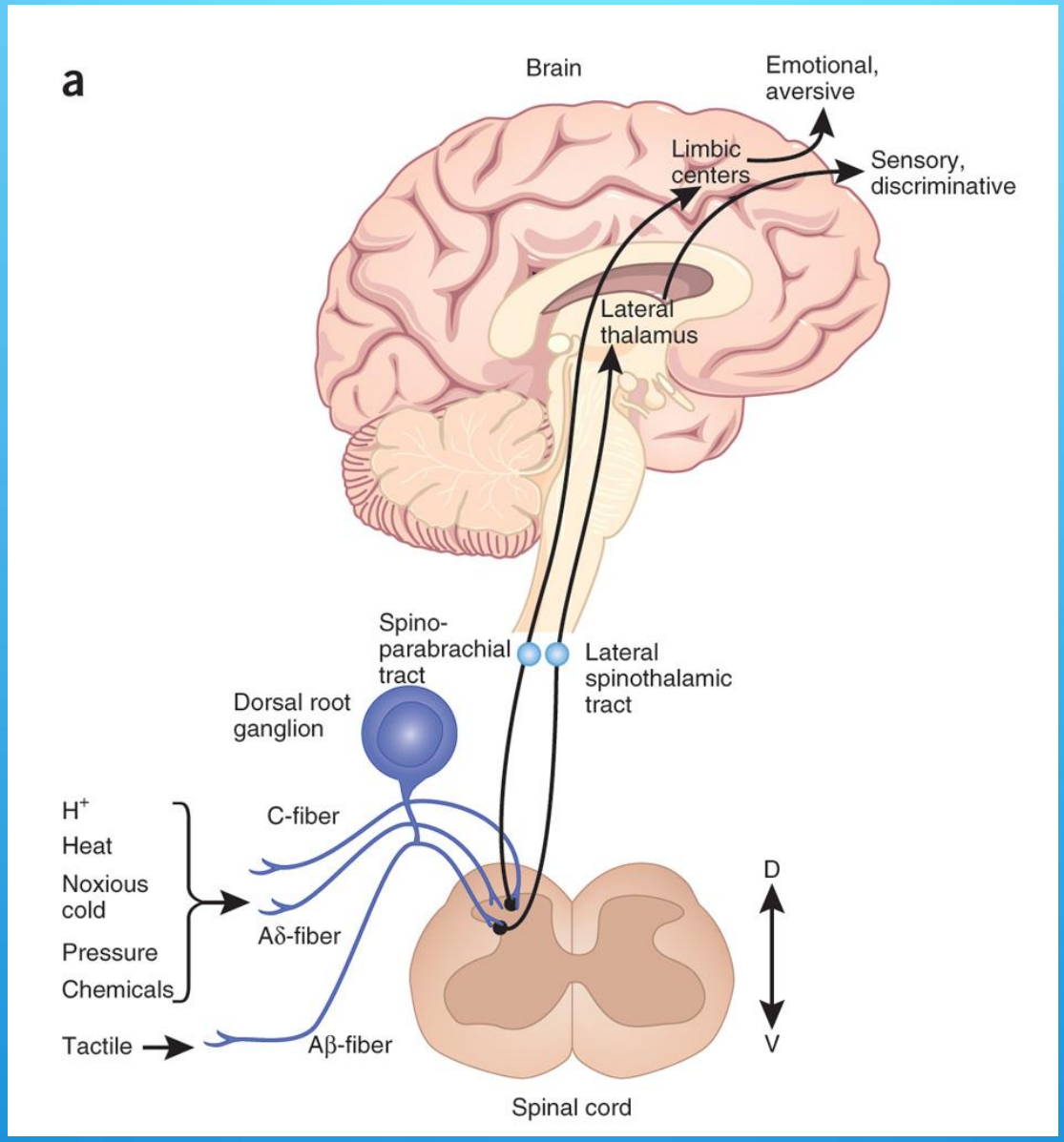


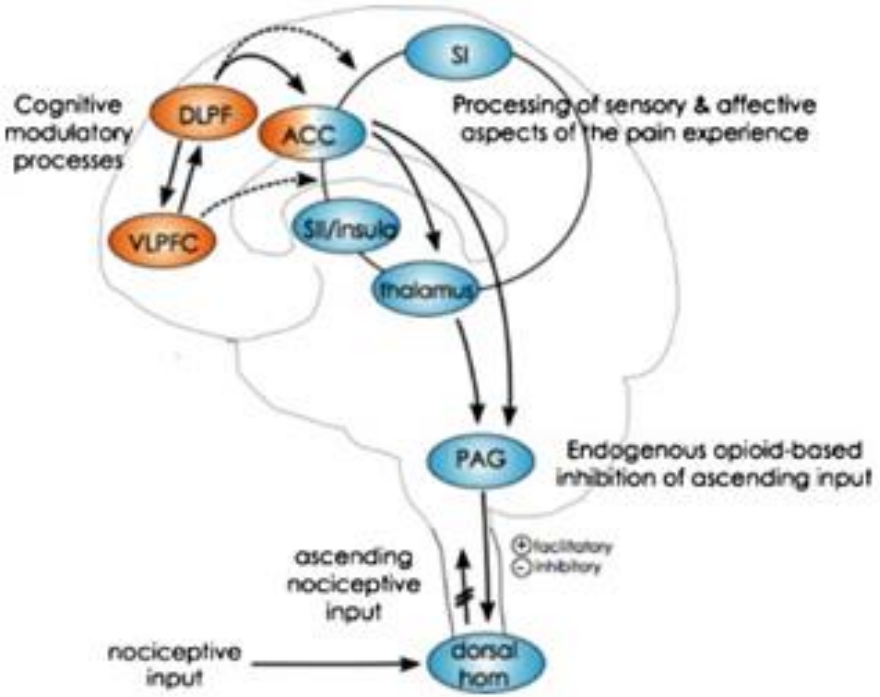
Why does pain become chronic?

Persistent acute stimulus becoming chronic	• Increased sensitivity of CNS to peripheral stimulus
Neuroplasticity	• Interaction between PNS and CNS results permanent changes in system
Memory of pain	• Somatosensory cortex changes
Genetic predisposition	

Peripheral and central interaction: The 'neuromatrix'

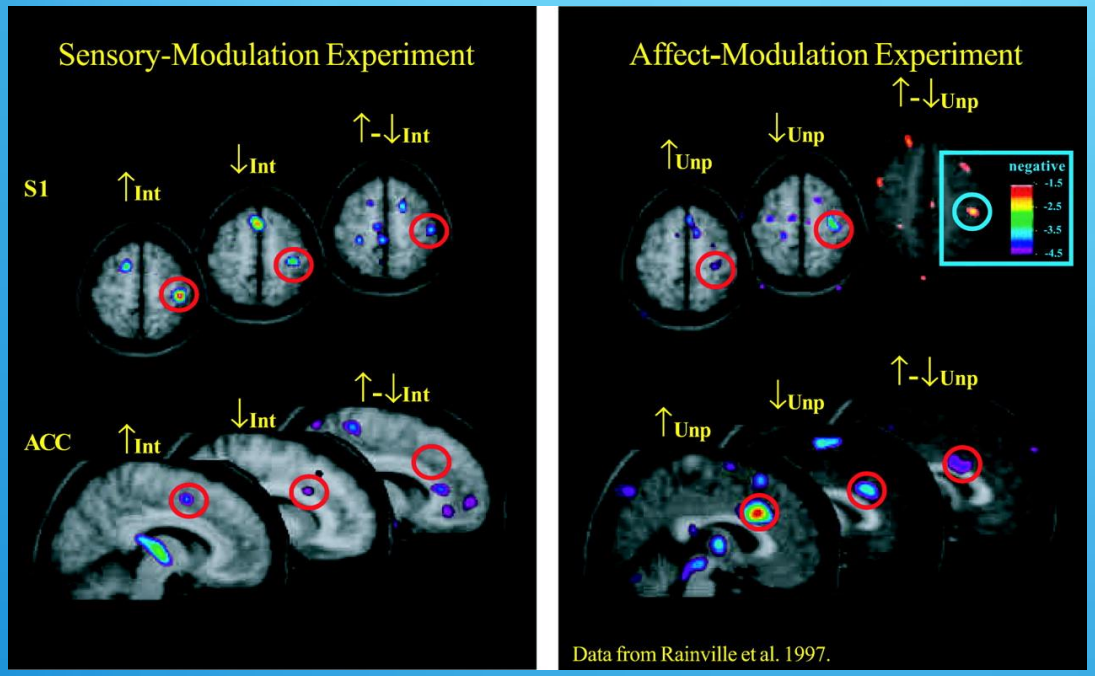



a
Brain
Emotional, aversive
Limbic centers
Sensory, discriminative
Lateral thalamus
Spino-parabrachial tract
Lateral spinothalamic tract
Dorsal root ganglion
H+
Heat
Noxious cold
Pressure
Chemicals
C-fiber
Aδ-fiber
Tactile
Aβ-fiber
D
V
Spinal cord



Possible neural pathways of cognitive **pain modulation**. Cognitive modulations of pain are related to activation of prefrontal brain areas such as the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and to the anterior cingulate cortex (ACC); shown in orange. These regions may modulate activation in afferent pain regions in the cortex (ACC, primary- and secondary somatosensory cortex, insula and thalamus), as well as the periaqueductal gray (PAG) and dorsal horns of the spinal cord; shown in blue. The DLPFC and VLPFC are connected to the ACC, which, in turn, projects to thalamus and the PAG, a core component of the descending pain modulatory system.

Brain activity
affective vs neurophysiological



>90% affective
<10% sensory

Cortical Representation of the Sensory Dimension of Pain AJP - JN Physiol **July 1, 2001** vol. 86 no. 1 **402-411**

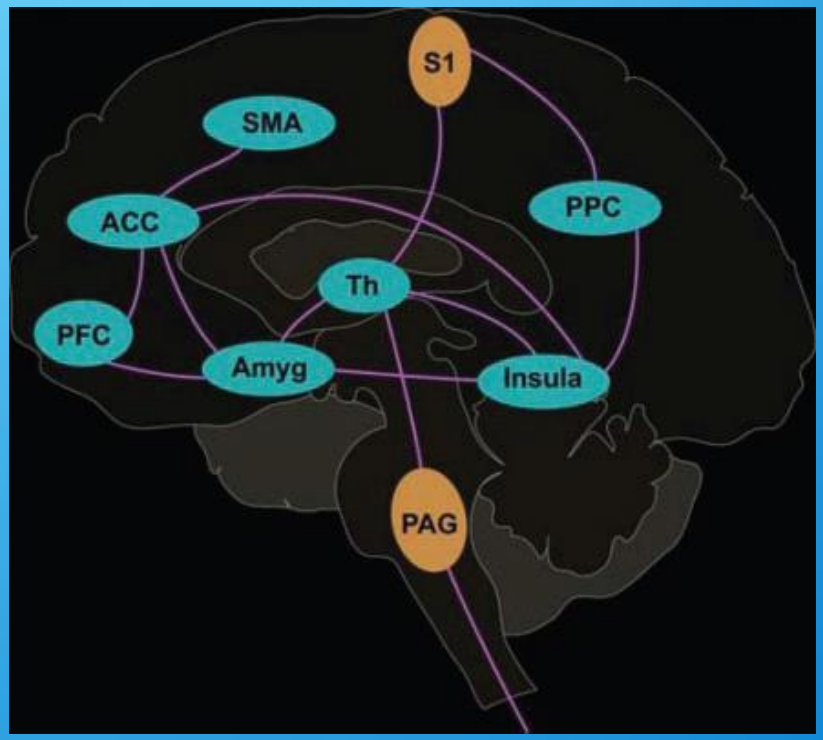
Ethan Kross [et] al., Proceedings National Academy of Science USA. Social rejection shares somatosensory representations with physical pain

Structural Brain Imaging: A Window into Chronic Pain.

Arne May. The Neuroscientist 17(2) 209-220:2011

- **Neuroplasticity**
- Cortical reorganisation
- Gray matter changes
- Central sensitisation
- Maladaptive plasticity
- Downward facilitation
- Downward inhibition

(Placebo effect)



Structural Brain Changes: Cause or Consequence of Chronic Pain?

- Numerous modulatory mechanisms have been postulated and altogether addressed as “neuronal plasticity” (Woolf and Salter 2000), and structural changes of the brain need to be added to this list (May 2008)
- Gray matter changes The key message of all three studies is that the main difference in the brain structure between pain patients and controls may recede when the pain is cured
- The impact of pain killers and other medications on morphometric findings is simply not known.
- Chronic nociceptive input leads to intra cortical remodelling
- We need to improve our understanding of experience-dependent changes in cortical plasticity as this will have vast clinical implications for the treatment of chronic pain.

Loss gray matter

- It is indeed remarkable that the alterations (i.e., decrease in gray matter) seen in the ACC in migraine patients are similar to a decrease in this region in tension-type headache (Schmidt-Wilcke et al., 2005), posttraumatic headache (Obermann et al., 2009), idiopathic facial pain (Schmidt-Wilcke et al., 2010), chronic back pain (Schmidt-Wilcke et al 2006), and chronic phantom pain (Draganski, Moseret al 2006).

- **Gray matter** volume reduction reflects **chronic pain** in trigeminal neuralgia.Obermann M, Rodriguez-Raecke R, Naegel S, Holle D, Mueller D, Yoon MS, Theysohn N, Blex S, Diener HC, Katsarava Z
- Structural Brain Anomalies and **Chronic Pain**: A Quantitative Meta-Analysis of **Gray Matter** Volume. Smallwood RF, Laird AR, Ramage AE, Parkinson AL, Lewis J, Clauw DJ, Williams DA, Schmidt-Wilcke T, Farrell MJ, Eickhoff SB, Robin DA. J **Pain**. 2013 May 16.

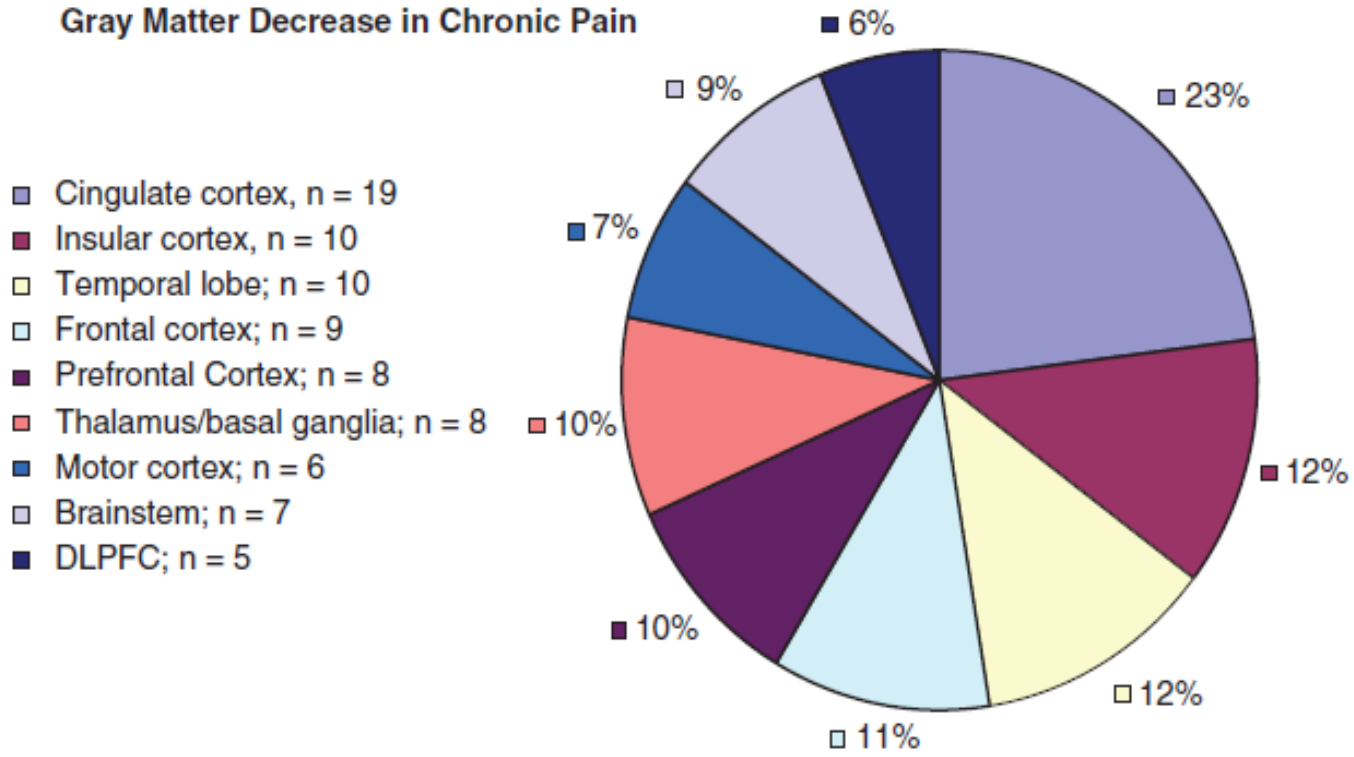
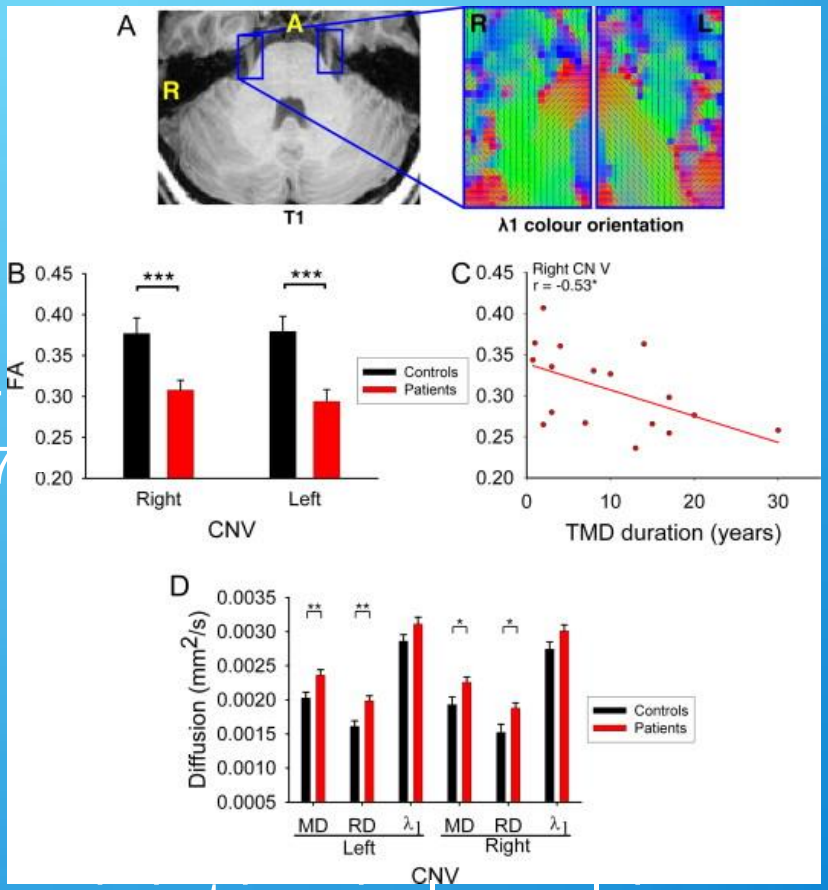


Figure 3. Gray matter decrease in 30 studies including a total of 839 patients. Compared with controls, 30 areas in the brain have been identified (increase and decrease of gray matter). Most areas are only cited by one or two studies. Only the brain areas being cited by at least five independent manuscripts are displayed (n corresponds to number of studies citing this brain area), and the percentages correspond to these nine structures. The most prominent findings are decreases in the cingulate cortex, the insular cortex, the temporal lobe, the frontal cortex, and the prefrontal cortex. DLPFC = dorsolateral prefrontal cortex.

Trigeminal nerve

- Reduction gray + white matter TMD

White matter brain and trigeminal nerve abnormalities in temporomandibular disorder Massieh Moayedi. PAIN Vol 153,7,2012,1467-1477



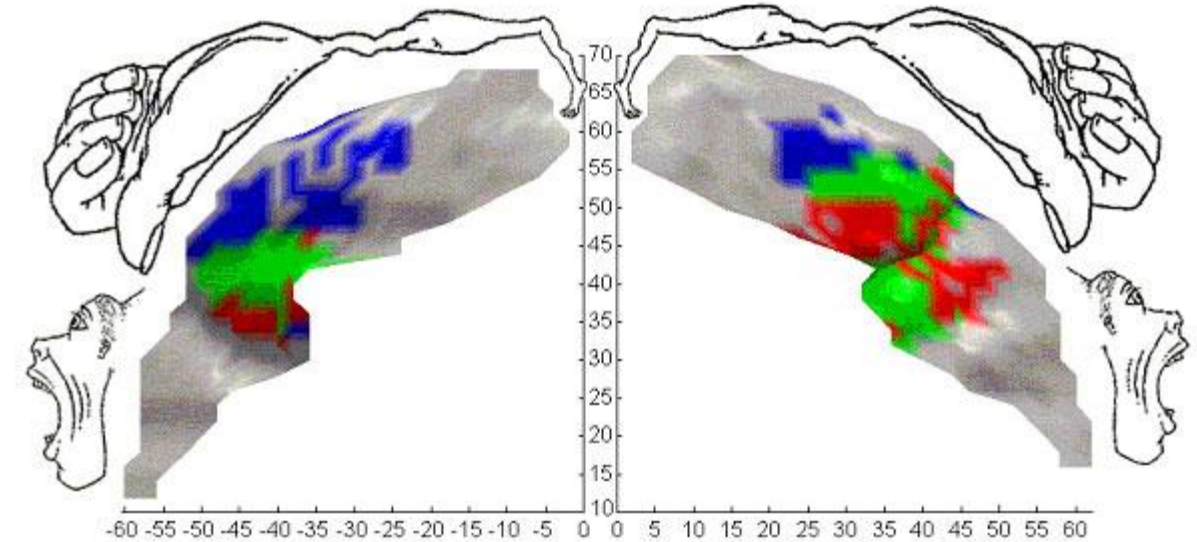
- Gray matter reduction in TN

Gray matter volume reduction reflects chronic pain in trigeminal neuralgia. Obermann M, Rodriguez-Raecke R, Naegel S, Holle D, Mueller D, Yoon MS, Theysohn N, Blex S, Diener HC, Katsarava Z.Neuroimage. 2013 Jul 1;74:352-8. doi: 10.1016

Cortical reorganisation

A recent study suggests that brain changes in amputees may be pain-induced, questioning maladaptive plasticity as a neural basis of phantom pain. These findings add valuable information on cortical reorganization after amputation.

Flor H, Diers M, Andoh J **The neural basis of phantom limb pain.** Trends Cogn Sci. 2013 Apr 19. pii: S1364-6613(13)00080-6. doi: 10.1016/j.tics.2013.04.007. [Epub ahead of print]



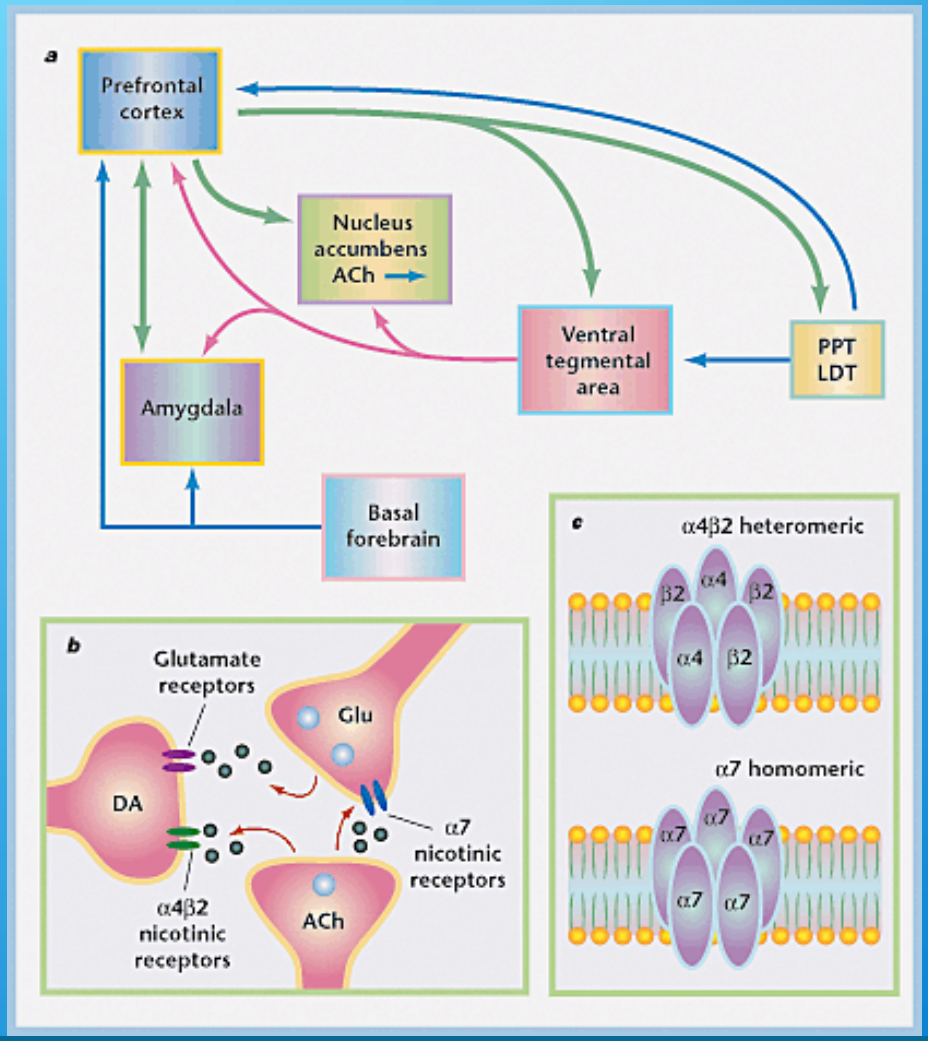
Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity

- Facilitation
- Augmentation
- Potentiation
- Amplification

=hypersensitivity

Alban Latremoliere& Clifford J. WoolfCentral Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity.

The Journal of Pain Volume 10, Issue 9 , Pages 895-926, September 2009

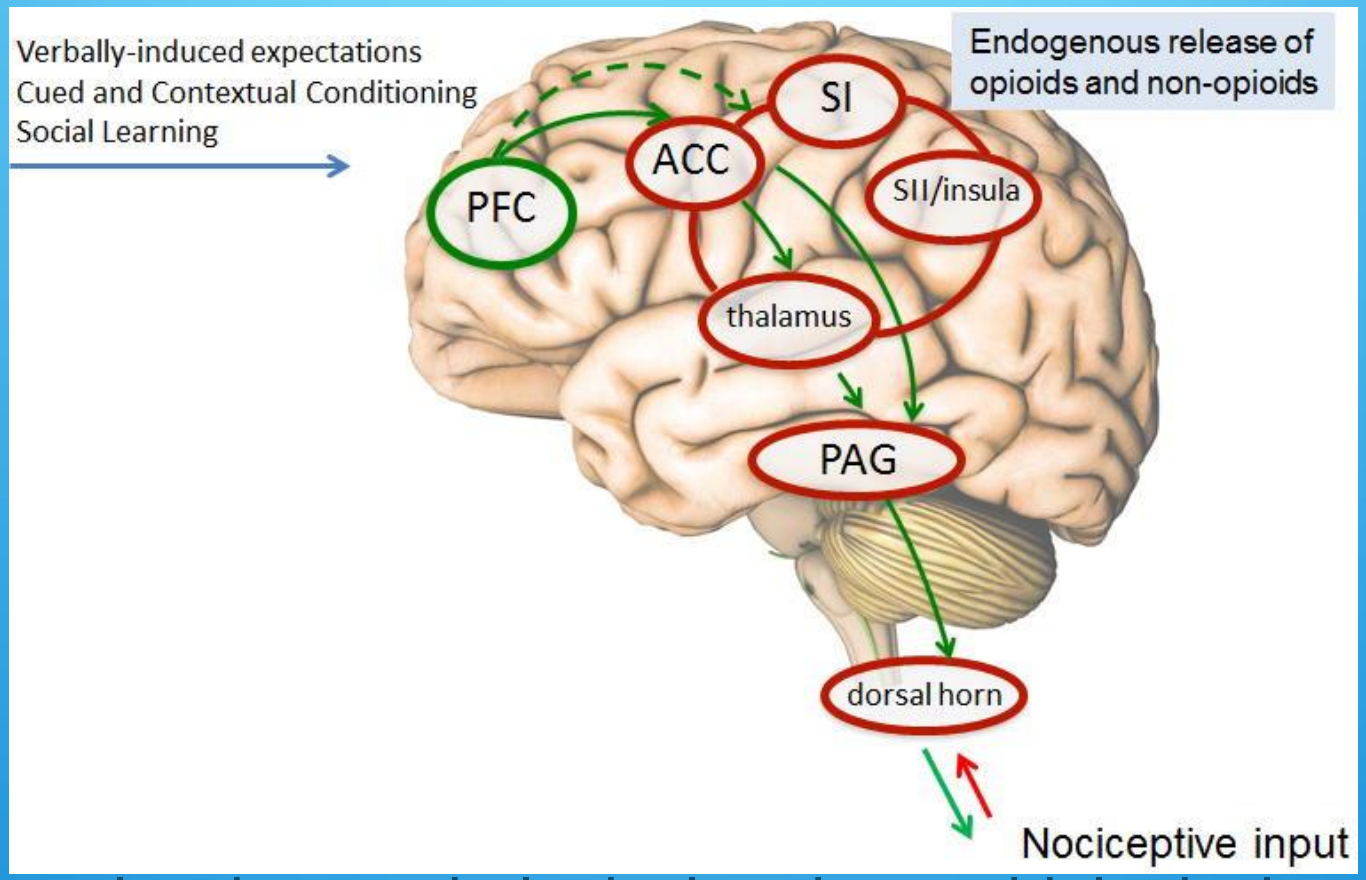


Maladaptive plasticity, memory for pain

Flor H. **Maladaptive plasticity, memory for pain and phantom limb pain: review and suggestions for new therapies.** Expert Rev Neurother. 2008 May;8(5):809-18.

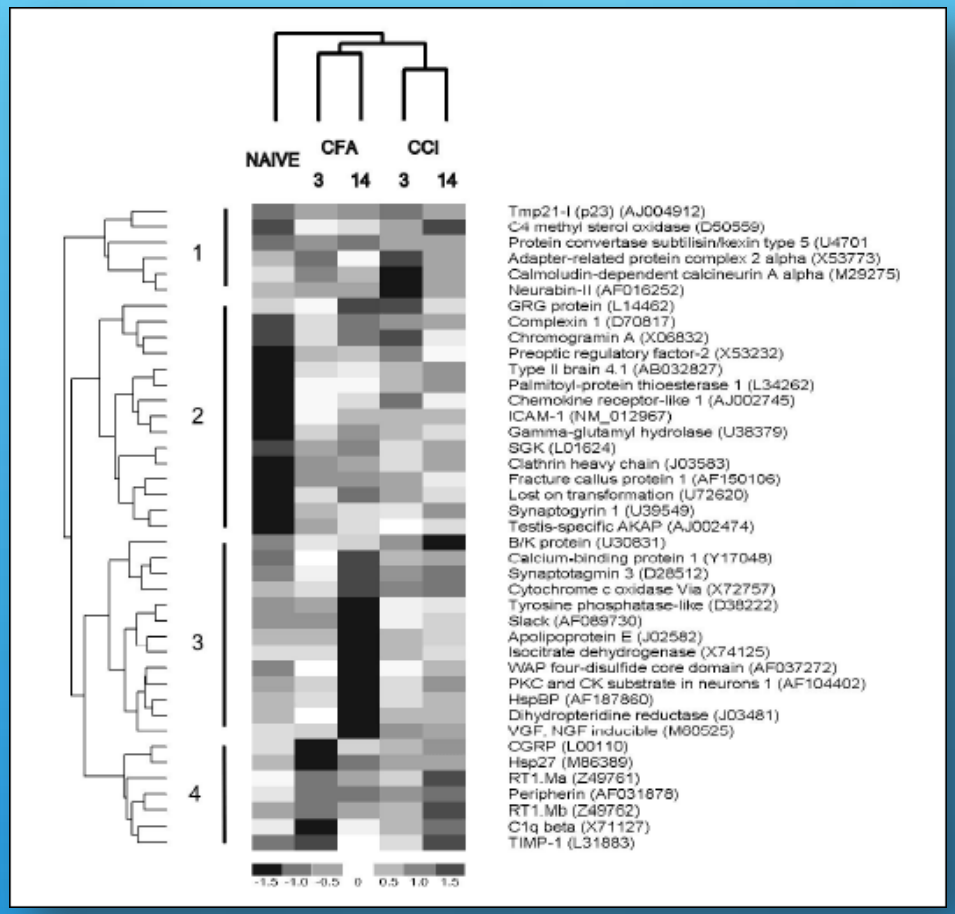
- Phantom limb pain is associated with plastic changes along the neuraxis
- Changes in the cortical representation of the affected limb
- Mechanisms underlying these maladaptive plastic changes are related **to a loss of GABAergic inhibition, glutamate-mediated long-term potentiation-like changes** and structural alterations such **as axonal sprouting**
- Behavioral interventions, stimulation, feedback and pharmacological interventions that are designed to reverse these maladaptive memory traces

Placebo effect



Placebo analgesia: psychological and neurobiological mechanisms. Colloca L, Klinger R, Flor H, **Bingel U**. Pain. 2013 Apr;154(4):511-4. doi: 10.1016/j.pain.2013.02.002. Epub 2013

Genetics and pain



- Six children from three related Pakistani families feel no physical pain
- Although capable of feeling other sensations like warm and cold they have a lack of pain perception have.
  - All six have had lip injuries
  - Two lost one-third of their tongues
  - Most suffered fractures or bone infections
  - Some have been scalded by boiling liquids or steam
  - Others burned from sitting on radiators
- SCN9A gene polymorphism resulting in Nav 1.7 sodium channel deficiency

Genetics of pain

- Red heads have more pain
- Melanocortin 1 receptor def
- 20% increase pain
- Melanocortin-1 Gene for Red Hair and Pain Tolerance
- “It does appear that redheads have a significantly different pain threshold and require less anaesthetic to block out certain pains,”
- Muopoid receptor

Candidate genes so far

- **COMT** (Seeman et al., 2005; Diatchenko et al., 2004)
- **DRD4** (Benjamin et al., 1996, Ebstein et al., 1996)
- **GCH1** (Tegeder et al., 2006)
- **CYP2 D6** (DeLeon et al., 2003; Ammon-Treiber et al., 2003)
- **DAT1** (Mill et al., 2006)
- **OPRM** (Fillingim et al., 2005, Kim et al. 2004)
- **TRPV1** (Kim et al. 2006)
- **IL1** (Solovieva et al., 2004)
- **IL6** (Noponen-Hielta et al., 2005)
- **SCN9A** (Cox et al., 2006)

The future of pain genetics

Improved diagnostics and patient care	• (e.g. „customised“ medication) with side effect reduction, risk management
Cost of genetic analyses will decrease	
More information on biological functions of genes and proteins	
Increased interdisciplinary work	• (imaging genomics, proteomics, QST) • Epigenetics will receive increased attention
Increasing numbers of papers on pain genetics	

New conditions-novel research

- Neuropathic pain NePain
- CRPS
- BMS
- Acute pain V studies

Editorial

Painful Posttraumatic Trigeminal Neuropathy: A Recently Recognized Entity

An unusual event recently occurred in the field of chronic orofacial pain. A new entity has been established through a few research papers and meetings of experts. Different specialists have known for some time that surgery and other traumatic events may injure the trigeminal nerve and provoke symptoms. Nerve damage may occur during Caldwell-Luc intervention, orthognathic mandibular advancement surgery, extrusion of root canal filling materials, implant surgery, and various traumatic events such as facial fractures and therapeutic radiation; third molar removal is the most frequent cause.[1] Several branches of the mandibular or maxillary division of the trigeminal nerve could be involved, such as the infraorbital nerve, the superior alveolar nerves, and most frequently the lingual and inferior

indicated that the 20 cases of PPTTN found among 245 cases of chronic orofacial pain tended to cluster.[7] This was in line with a recent study performed on 328 patients with chronic orofacial pain that indicated that over 12% of the cases were PPTTN.[8] These two studies pointed to a much larger prevalence than what was previously suspected, even if these samples were far from being representative of the general population since they came from tertiary care centers. The contribution of the different specialties to the incidence of PPTTN has been recently detailed.[2,9,10]

2. *Description of diagnostic criteria for PPTTN:* This has much improved due to recently performed studies. Quantitative sensory testing associated with electrophysiological exploration have better

Woda A J Orofacial Pain Vol 27 No 2 2013

- Geber C, Baumgärtner U, Schwab R, Müller H, Stoeter P, Dieterich M, Sommer C, Birklein F, Treede RD.

Revised definition of neuropathic pain and its grading system: an open case series illustrating its use in clinical practice. Am J Med.2009 Oct;122(10 Suppl):S3-12.

- Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG) as "pain arising as direct consequence of a lesion or disease affecting the somatosensory system," and a grading system of "definite," "probable," and "possible" neuropathic pain has been introduced

Haanpää M, et al

NeuPSIG guidelines on neuropathic pain assessment.

Pain. 2011 Jan;152(1):14-27. doi: 10.1016/j.pain.2010.07.031. Epub 2010 Sep 19.

- Ne Pain questionnaire screen
- Clinical assessment- sensory testing
- QST -Measurement of trigeminal reflexes mediated by A-beta fibers can be used to differentiate symptomatic trigeminal neuralgia from classical trigeminal neuralgia. Measurement of laser-evoked potentials is useful for assessing function of the A-delta fiber pathways in patients with neuropathic pain
- No MRI
- Biopsy if small fibre neuropathy suspected
- validated neuropathic pain quality measures and assessment of sleep, mood, functional capacity and quality of life are recommended

Presentation of neuropathic pain

- Mixed anaesthesia, hypoaesthesia, hyperaesthesia, allodynia and hyperalgesia
- Every single sensory abnormality occurred in each neurological syndrome, but with different frequencies: thermal and mechanical hyperalgesias were most frequent in complex regional pain syndrome and peripheral nerve injury, allodynia in postherpetic neuralgia

- Maier C et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain. 2010 Sep;150(3):439-50

Mechanism NePain

- **Molecular changes in nociceptive neurons**
- **Adjacent uninjured neurons** driven by substances released by dying cells
- Hyperactivity in nociceptors in turn induces secondary changes (hyperexcitability) in processing neurons in the spinal cord and brain.=**central sensitization**
- Neuroplastic changes in the central **descending pain modulatory systems** (inhibitory or facilitatory)

Baron R **Neuropathic pain: a clinical perspective.** Handb Exp Pharmacol. 2009;(194):3-30.

CRPS

Complex regional pain syndrome (CRPS), formerly known as Sudeck's dystrophy and causalgia, is a disabling and distressing pain syndrome.

CRPS may develop following fractures, limb trauma, or lesions of the peripheral or central nervous system.

The clinical picture comprises a characteristic clinical triad of symptoms including autonomic (disturbances of skin temperature, color, presence of sweating abnormalities), sensory (pain and hyperalgesia), and motor (paresis, tremor, dystonia) disturbances.

The diagnosis is mainly based on clinical signs. A very recent study showed that patients exhibited a gray matter decrease in the right insula, right ventromedial prefrontal cortex, and right nucleus accumbens (Geha and others 2008).

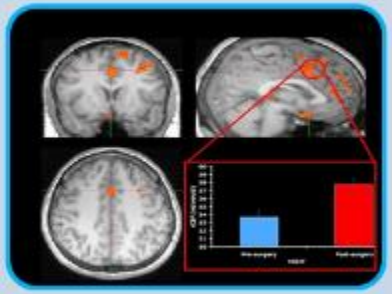
CRPS of the Trigeminal system?

Complex regional pain syndrome following trigeminal nerve injury: report of 2 cases. Khan J, Heir G, Benoliel R, Eliav E. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Jul;116(1):123.

Complex Regional Pain Syndrome Reflex Sympathetic Dystrophy

- Sympathetic Nerve Blocks
- Neurostimulation Therapy
- Pharmacological Intervention
- Complex regional pain syndrome is an uncommon form of chronic pain that usually affects an arm or leg. Complex regional pain syndrome typically develops after an injury, surgery, stroke or heart attack, but the pain is out of proportion to the severity of the initial injury, if any.
- The cause of complex regional pain syndrome isn't clearly understood. Treatment for complex regional pain syndrome is most effective when started early. In such cases, improvement and even remission are possible. Neurostimulation Therapy represents a great advancement in the treatment of CRPS

Peripheral receptors



Central pain pathway

Genetics

Research

Work ongoing
Trigeminal pain: an update

- Inflammatory nociceptive pain
  - *Dental Pain Peripheral + genetics*
  - *Post surgical pain Genetics,Peripheral and central*
- Neuropathic pain
  - Post Traumatic Neuropathy *Genetics, Peripheral and central psychometrics*
  - Trigeminal autonomic cephalgias *Genetics, Peripheral and central*
  - Trigeminal neuralgia *Genetics, Peripheral and central*
  - Burning mouth *Genetics, Peripheral and central*

Research

Unravelling toothache

Immortalised cell line of odontoblastic

+ve markers TRPA1, TRPV1 and TRPV4.

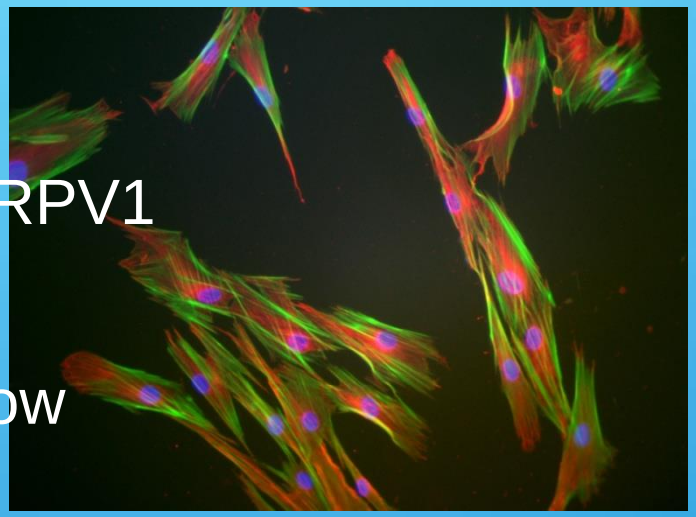
Microarray, RT-PCR, flow cytometry and

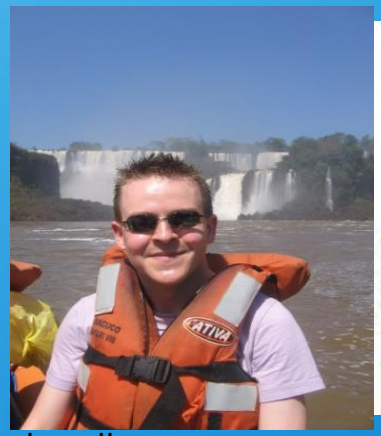
Calcium imaging studies

Obi Egbuniwe PhD St

Prof Lucy Di Silvio

Dr Andy Grant

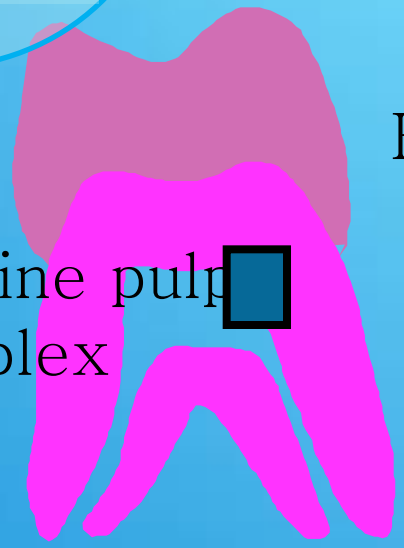




P16/P53 expression and telomerase activity in immortalized human dental pulp cells
Egbuniwe O., Idowu BD, Funes JM, Grant AD, Renton T, Di Silvio L (Tissue Engineering (IF = 4.5)

Research

Method Tissue sampling

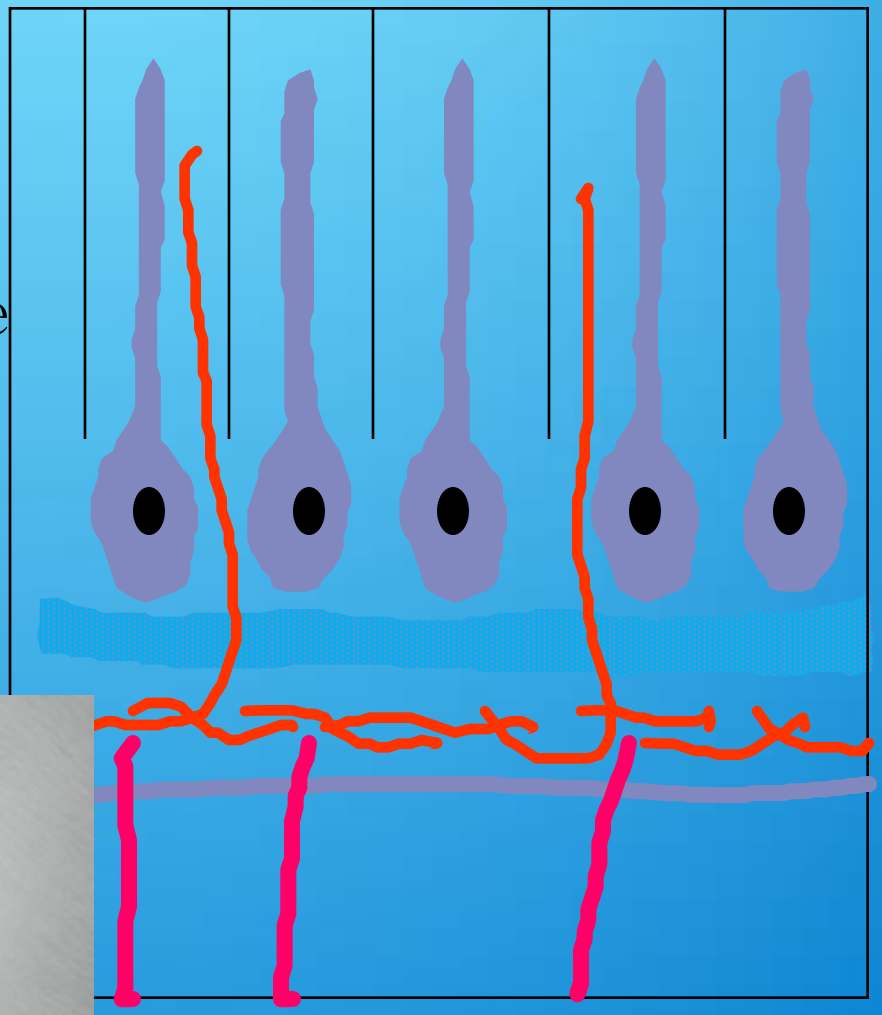


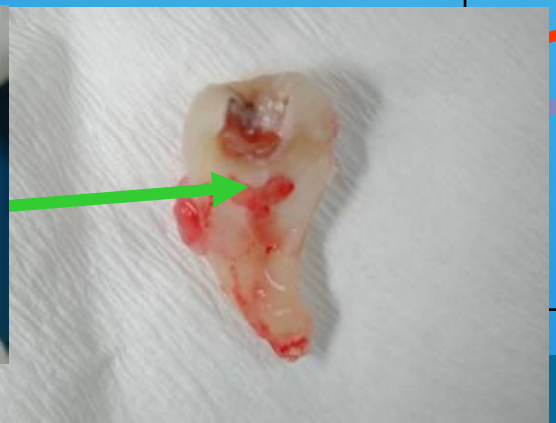
Dentine pulp complex

Enamel

Dentine

Pulp





Nociceptors in dental pulp

Research

•**Renton T**, Yiangou Y, McGurk M, Plumpton C, Tate S, Bountra C, Anand P. Presence of VR1 and P2X3 sodium channels in tooth pulp. J Orofacial Pain 2003;17:245-250**Renton T**, Yiangou Y, Plumpton C, Tate S, Bountra C, Anand P. Sodium channel Nav1.8 immunoreactivity in painful human dental pulp. BMC Oral Health. 2005 Jul 7;5(1):5.

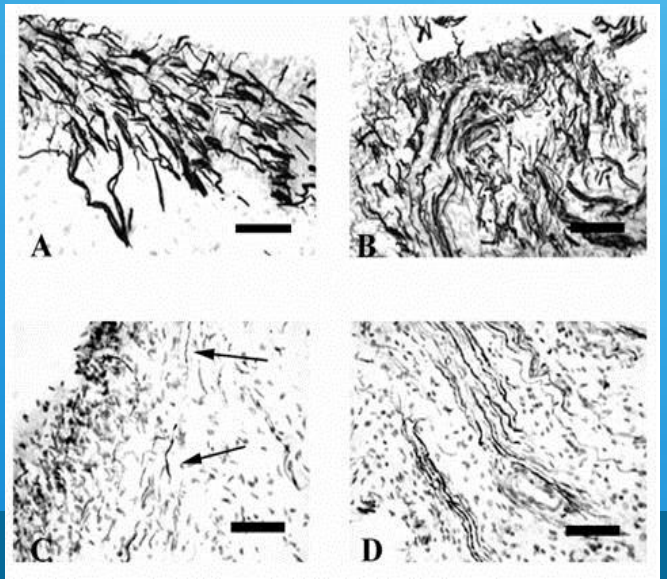
•Beneng K, **Renton T**, Yilmaz Z, Yiangou Y, Anand P. Sodium channel Nav1.7 immunoreactivity in painful human dental pulp and burning mouth syndrome. BMC Neurosci. 2010 Jun 8;11(1):71. [Epub ahead of print]PMID: 20529324

•Beneng K, Yilmaz Z, Yiangou Y, McPharland H, Anand P, **Renton T**. Sensory purinergic receptor P2X(3) is elevated in burning mouth syndrome. Int J Oral Maxillofac Surg. 2010 Apr 24. [Epub ahead of print]

•Beneng K, Renton T, Yilmaz Z, Yiangou Y, Anand P. Cannabinoid receptor CB1-immunoreactive nerve fibres in painful and non-painful human tooth pulp. J Clin Neurosci. 2010 Nov;17(11):1476-9. Epub 2010 Aug 11

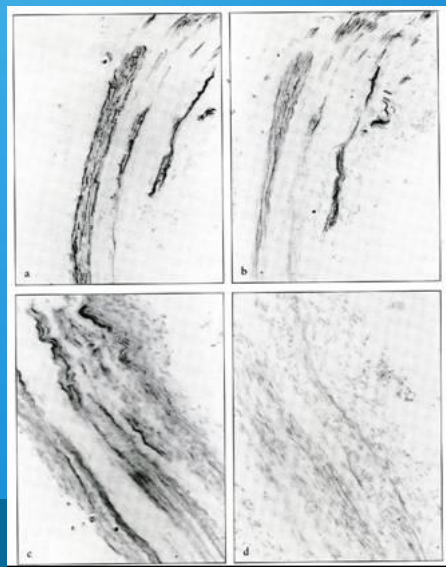
NF TRPV1

TRPV1
NaV 1.8
NaV 1.7
P2X3
CB1



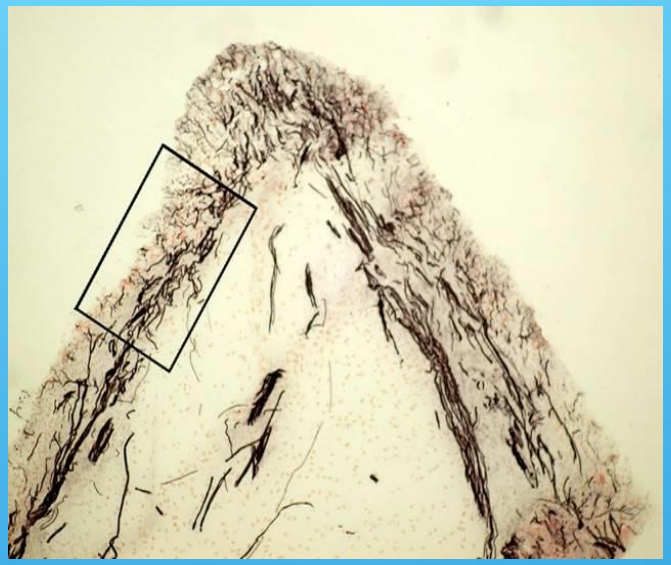
Painful pulp

Non painful p



Research

Gene expression novel targets



The microaaray data we got from painful and non painful teeth showed an up regulation of certain inflammatory markers and cytokines. We are looking at the effect of Substance P exposure on cellular activity

Work with **Prof Steve MacMahon & Dr Andy Grant**

Burning Mouth Syndrome

Incidence
Women 15:1
1-5%
Age >40-60yrs
Post menopausal

Features

Spontaneous onset

➢4month duration

Normal appearance

Supertasters/taste sensitivity

Research

BMS

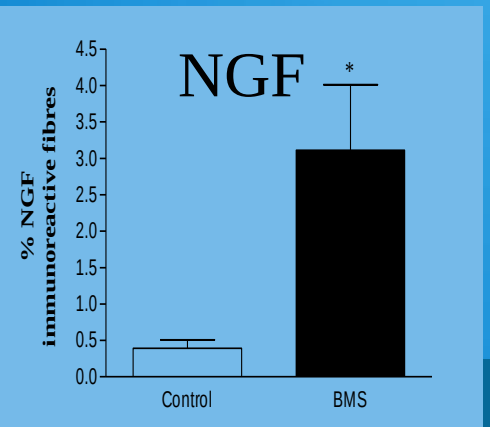
Dr Kiran Beneng PhD St

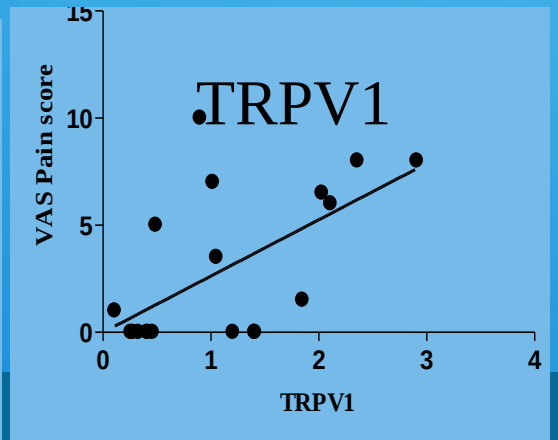
Prof Praveen Anand

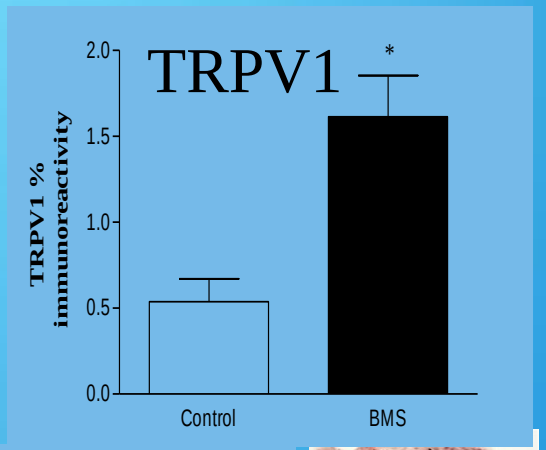
Dr Zehra Yilmaz

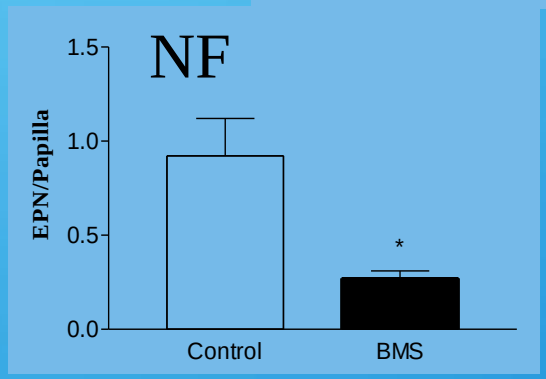
- Ongoing work TRPM8
- CB1, P2X3 and GABA receptors
- Imaging central pathways (CNS)

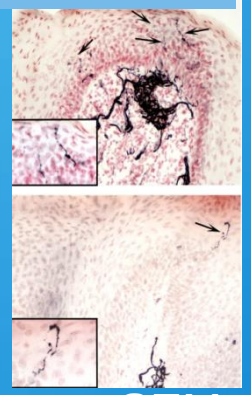
Dr Matt Howard







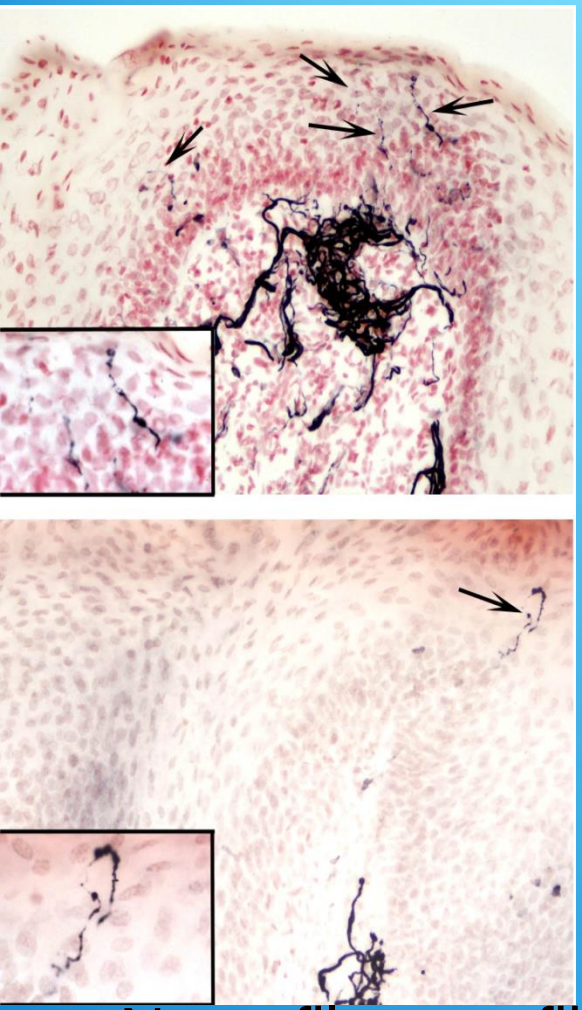


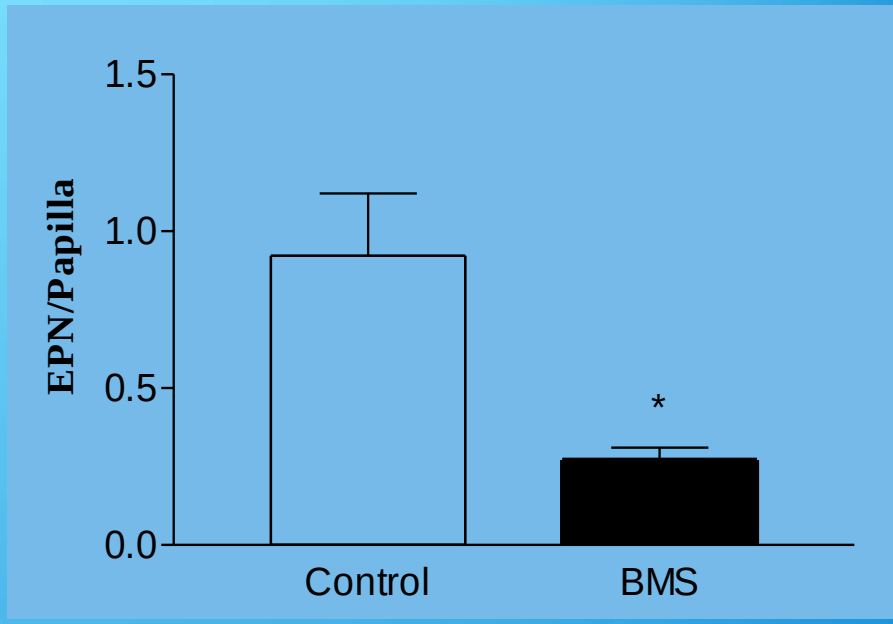


NF Bar charts of the mean ± SEM of epithelial nerve fibres per papilla in control and BMS tongue. * P <0.0001.

P =0.0006, Spearman r =0.55

NF 200 IR





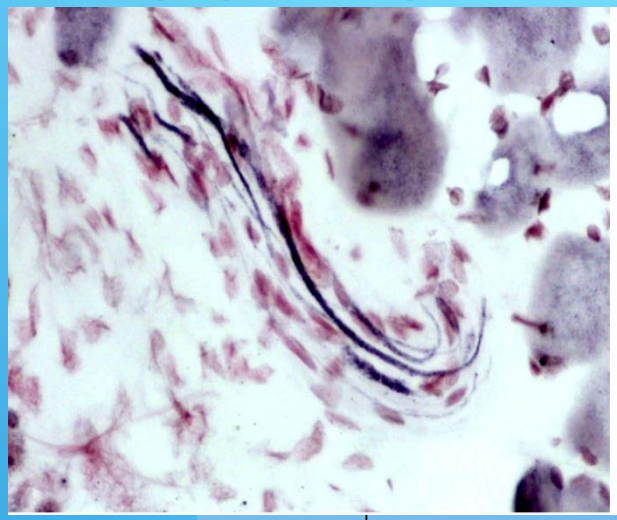
Bar charts of the mean ± SEM of epithelial nerve fibres per papilla in control and BMS tongue. * P <0.0001.

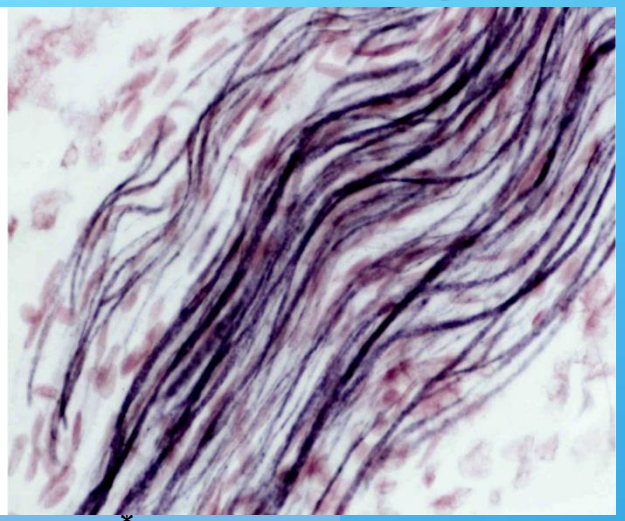
Neurofilament fibres in a Control (top panel) BMS tongue section (bottom panel) x20, and insets epithelial nerve fibres (arrowed) at magnification x40

NGF-IR

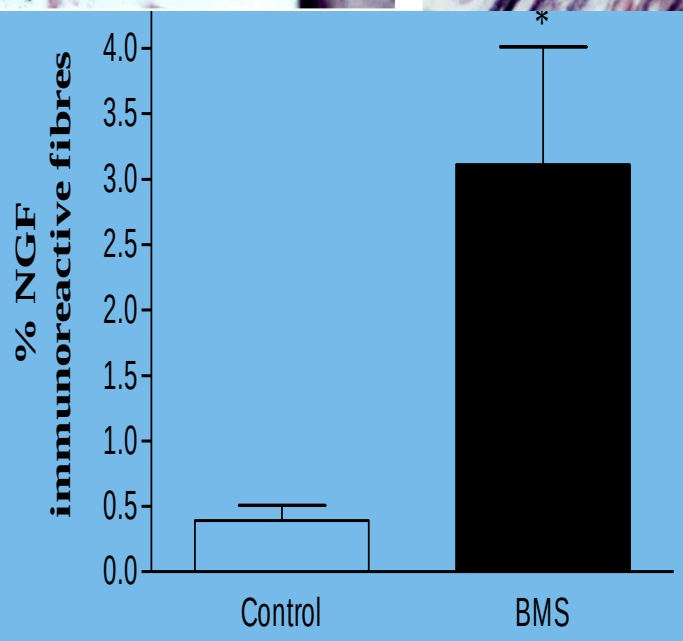
Control

BMS





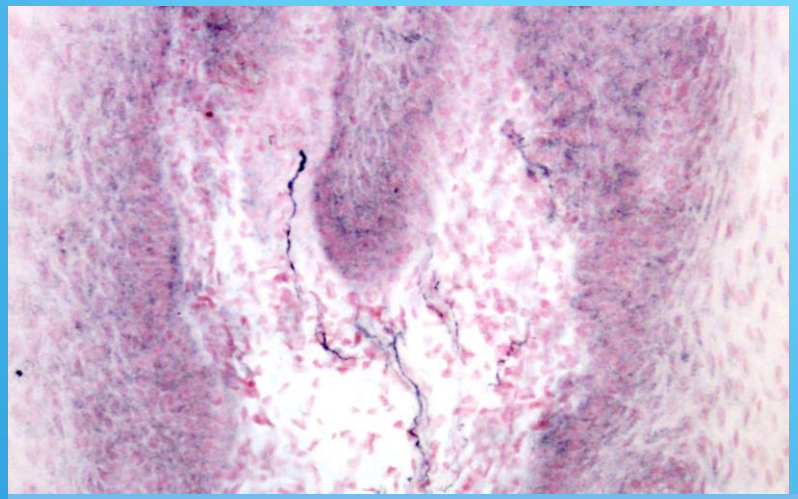
x40



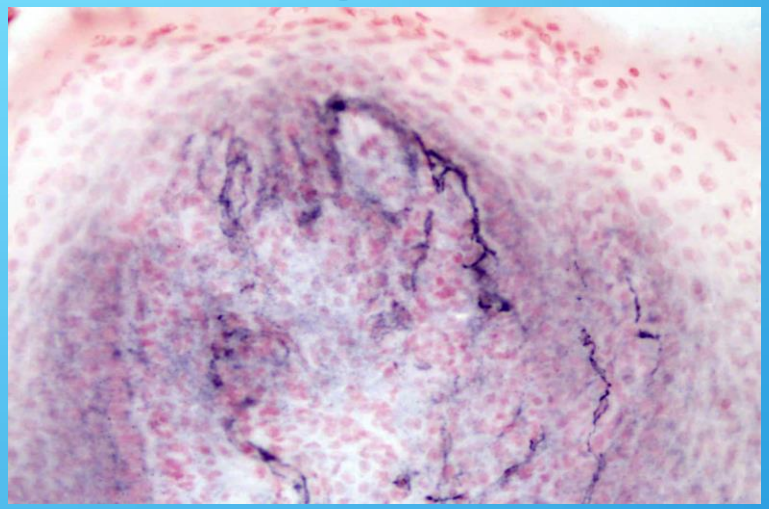
Bar charts of the mean ± SEM of % area of NGF nerve fibres in control (n=9) and BMS (n=9) tongue.
** P <0.0001*

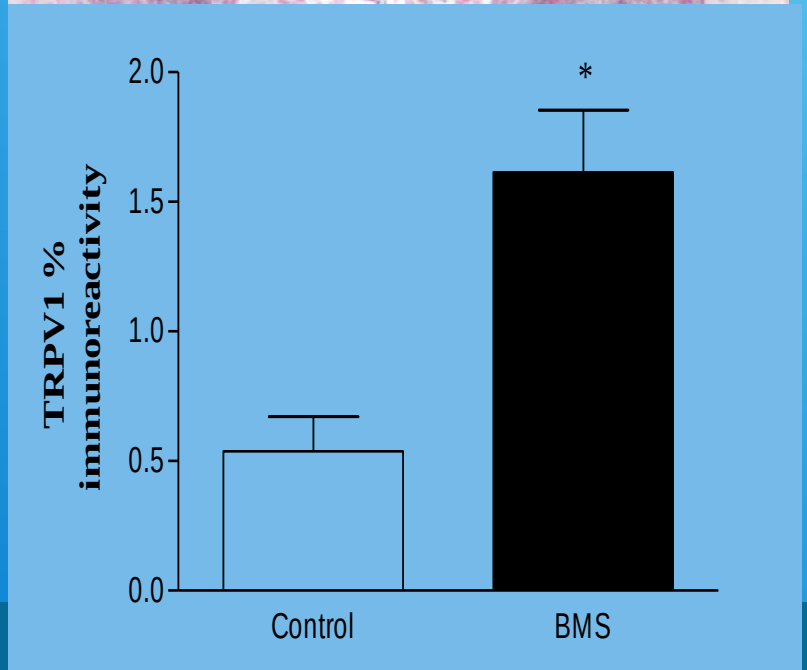
TRPV1 -IR

Control



BMS



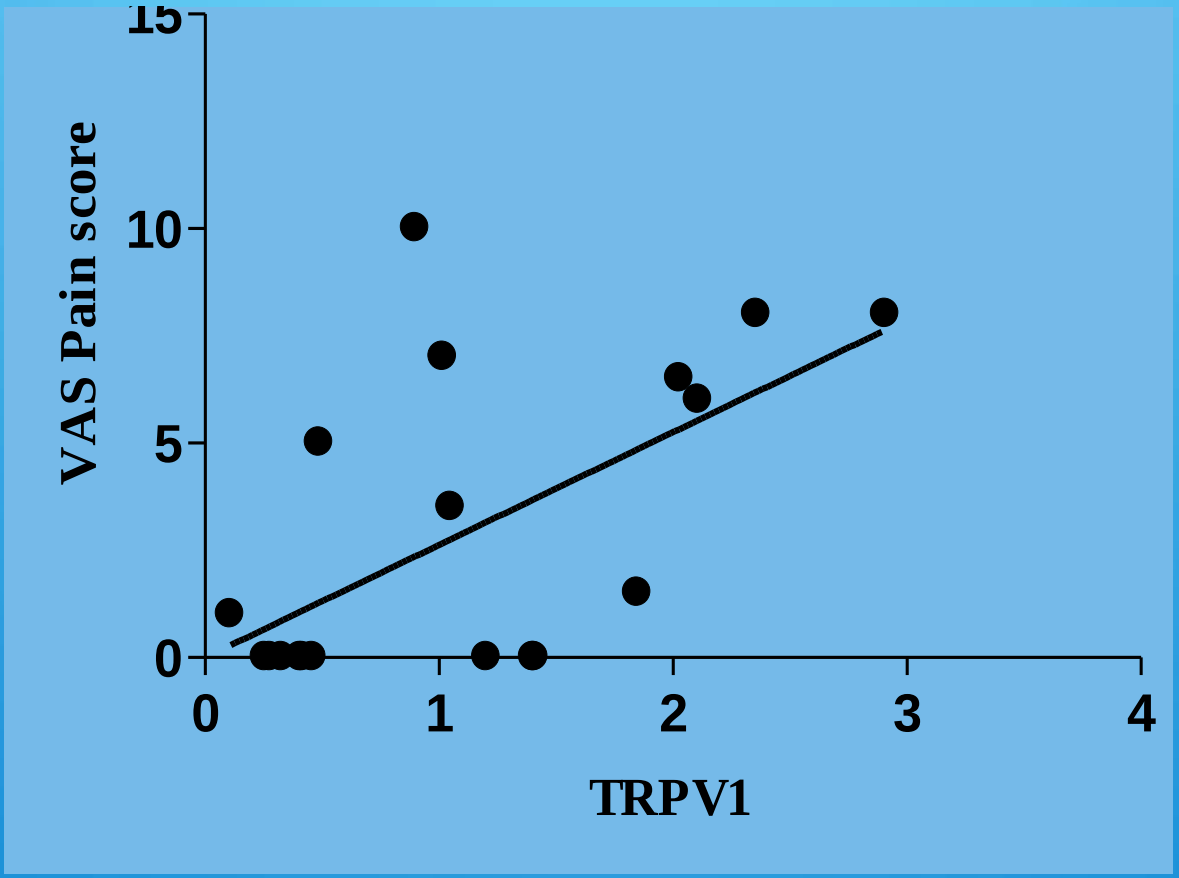


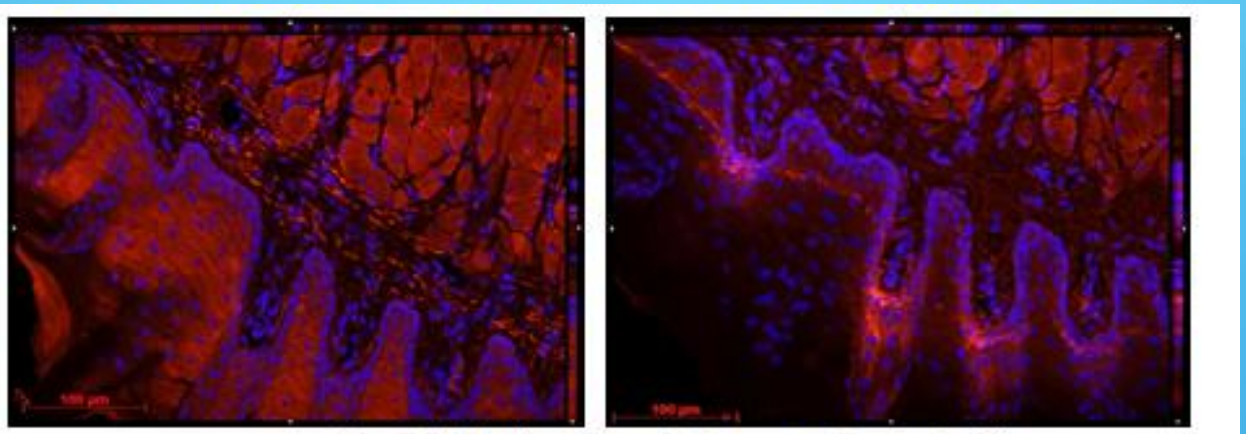
TRPV1 fibres staining in control and in BMS x20.

Bar chart shows the mean ± SEM of % area of TRPV1 fibres in control (n=10) and BM (n=10) tongue. * P =0.0011

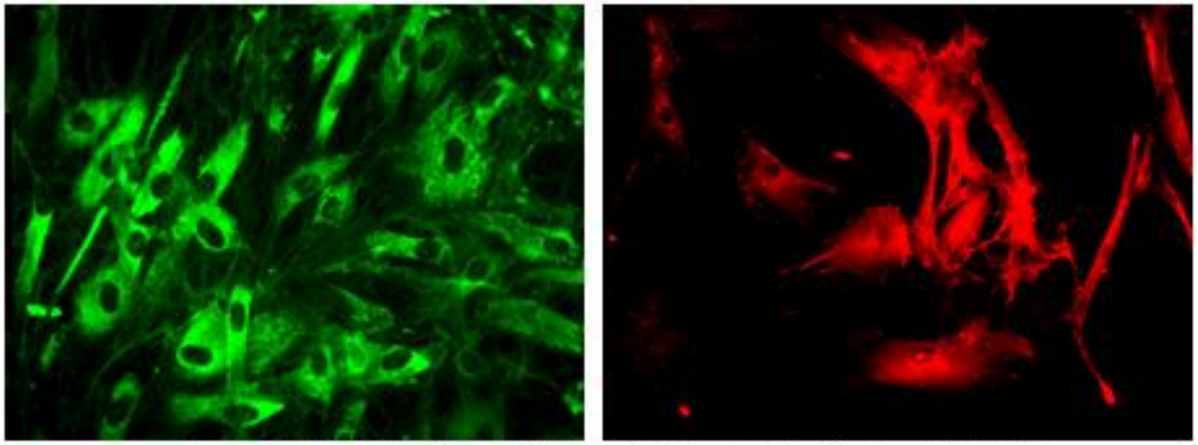
Correlation of TRPV1 fibre IR with VAS Pain score

P =0.0006, Spearman r =0.55





Immunohistochemical labelling of TRPA1 and TRPM8 positive rat tongue cells using Alexa Fluor© 488



Immunocytochemical labelling of collagen type 1 and dentine sialophosphoprotein positive human odontoblast cells

Post surgical acute pain

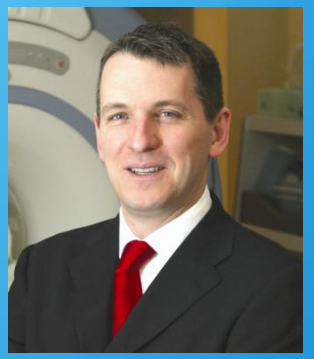
Research

Imaging post surgical pa

- TME most frequent model in acute pain trials

  (Moore et al., 2005)

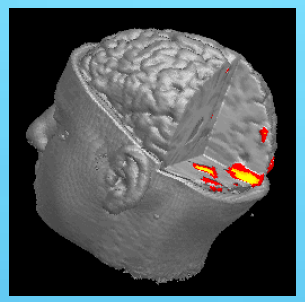
- 30-80% of patients suffer moderate to severe
  - pain post-operatively
  - (Popping 2008 & Apfelbaum 2003).



Prof Steve Williams IoP KCL Center Neuroscience imaging
Matt Howard, Kristina Krause, Anbarasu Lourdusamy
Gunter Schumann SGDP IoP
Nadine Khawaja IA PhD St

Pre-surgical visits

Ψ assessment & screening



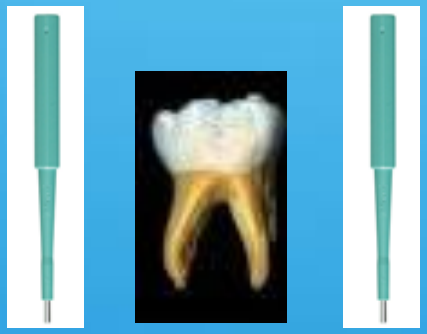
cASL assessment

post-scan RNA

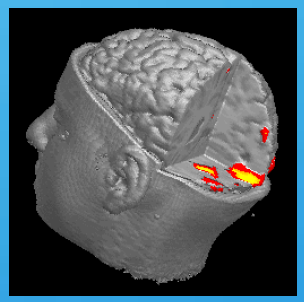
Surgical visits

Ψ assessment & screening

pre-surgery RNA



wisdom tooth extraction & mucosa

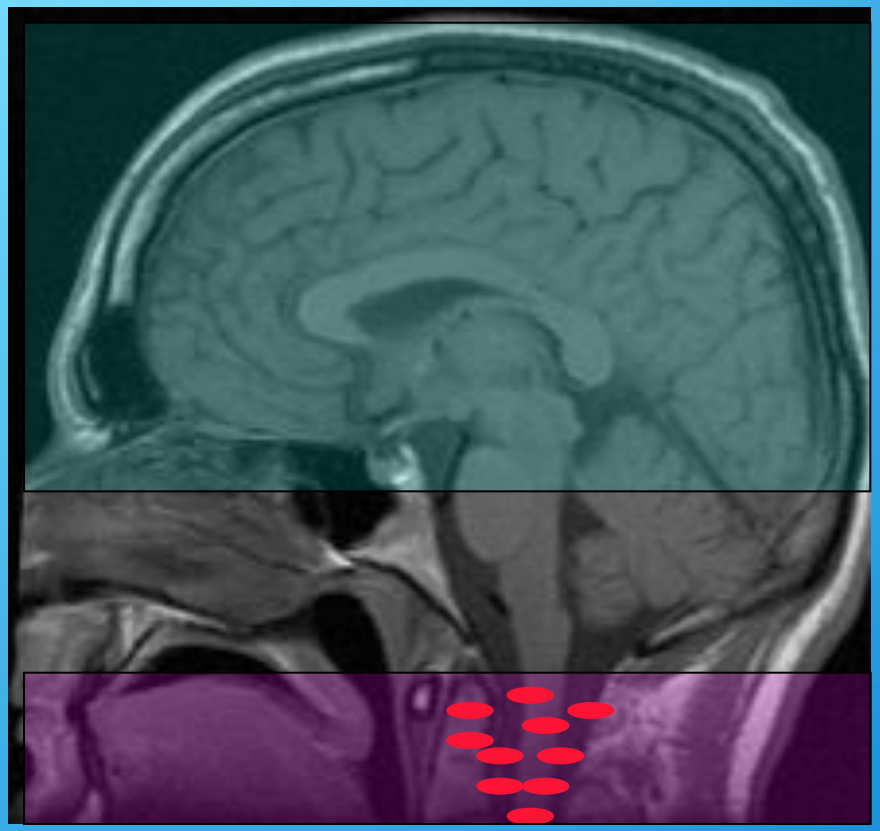


cASL assessment

post-scan/surgery RNA

Arterial spin labeling (cASL)

IMAGE ACQUISITION



MAGNETISATION OF BLOOD

- cASL can **quantify** cerebral blood flow (CBF) changes in active brain areas responding to pain
- examine ongoing TME pain to provide an **objective** measure of pain.

Measuring pain centre activity in the brain in man after third molar surgery

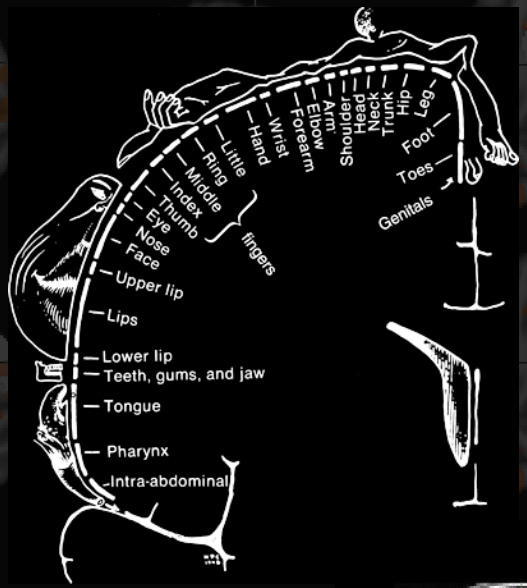
ACC

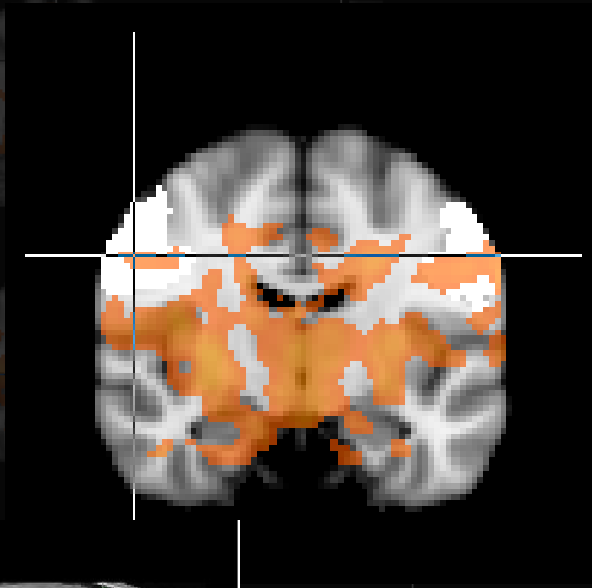
PCC

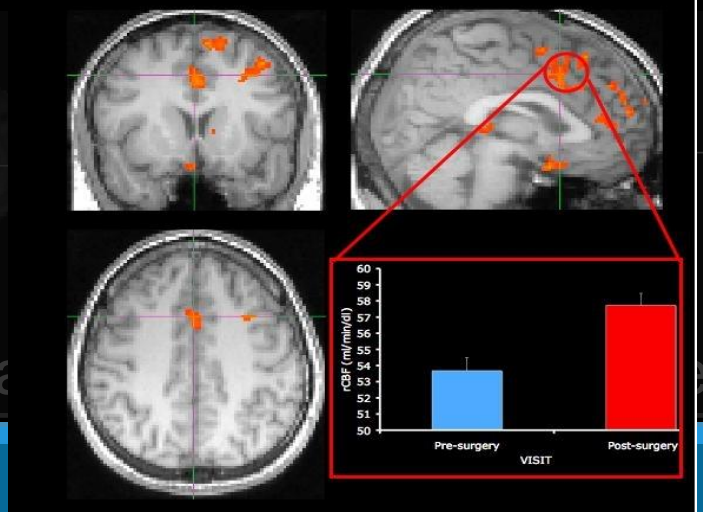
S1

S2

THAL

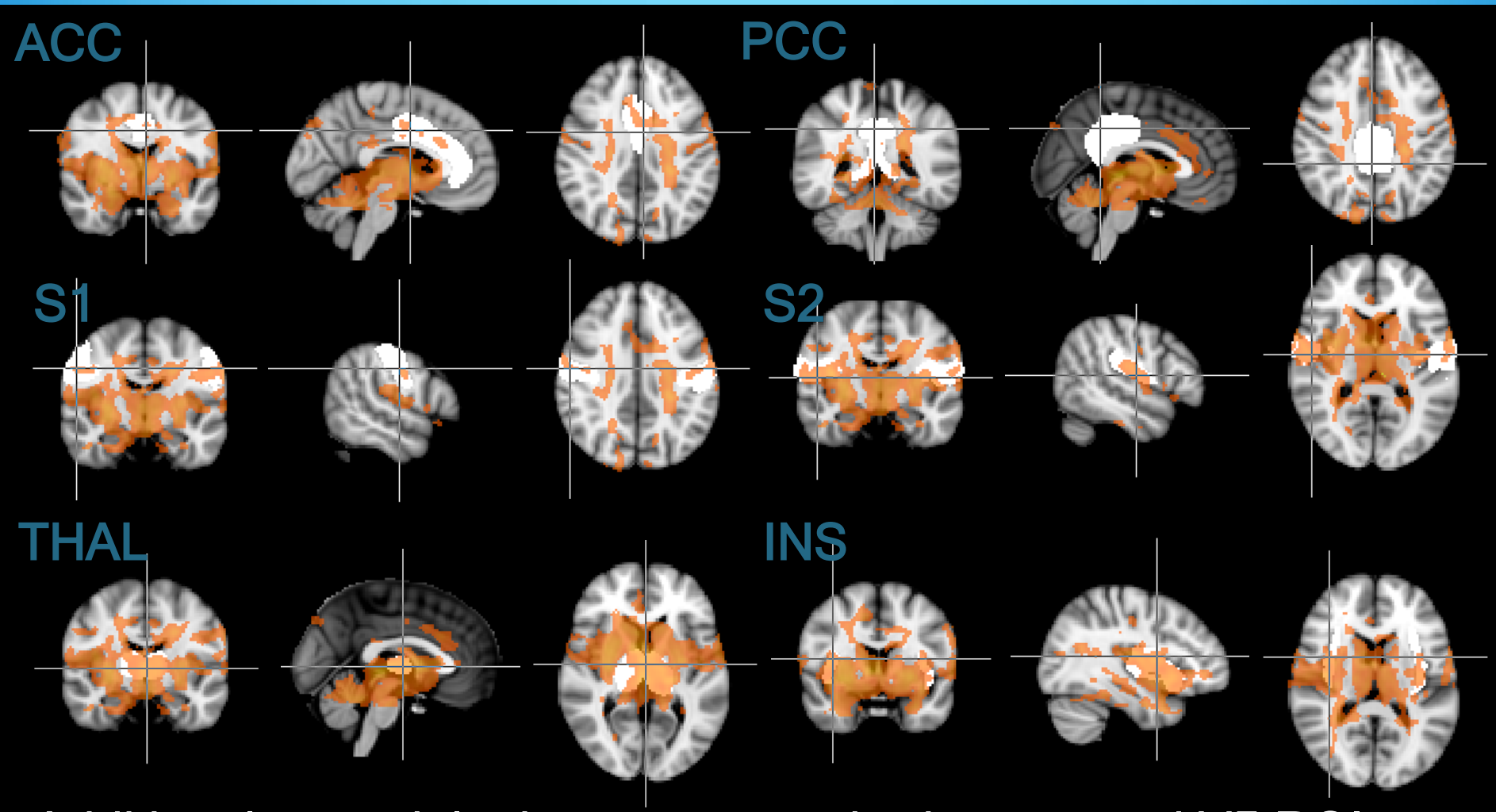






•Additional amygdala em, and V5 ROIs

Significant increases in post-surgical regional CBF in brain regions previously associated with pain (pain neuromatrix)

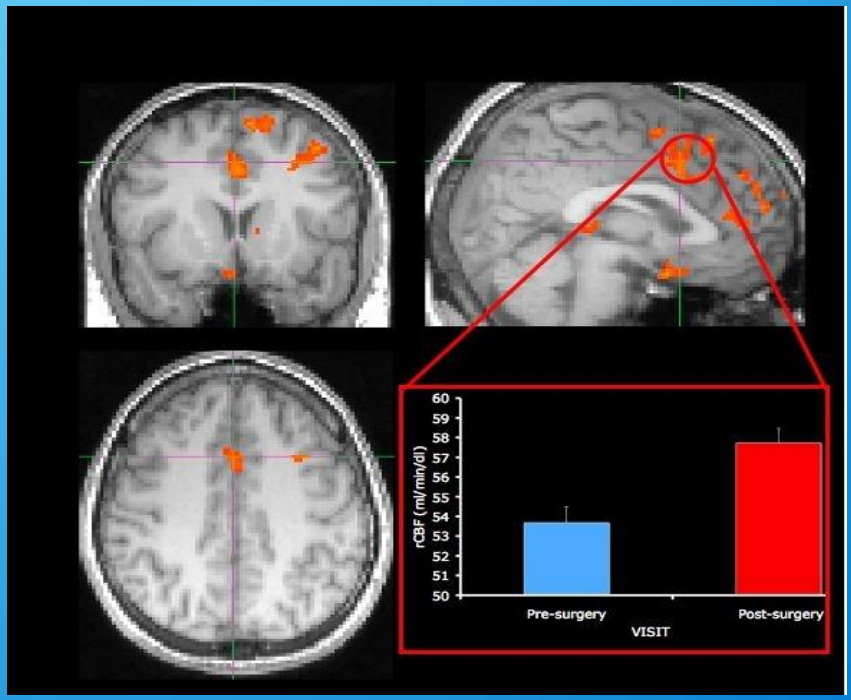


- Additional amygdala, hippocampus, brainstem, and V5 ROIs

Results

Significant increases in post surgical rCBF observed in;

- S1, S2, Thalamus, Insula, Anterior cingulate cortex
- Also in Amygdala and Hippocampus
- But NOT in control region
- Largest change seen in Thalamus
- No first or second order interaction of surgery for all ROIs
  - Presusrgery /post surgery
  - Side (left or right)
  - Hemisphere (left or right)



Genetics

- Post surgical pain (TMS)
- Burning mouth syndrome
- Post surgical painful neuropathy
- TN
- Cluster headaches, SUNCT and SUNA

Post surgical pain
Gene expression & VAS score relationships

- Correlation between 38 genes and VAS scores
- RED up regulated
- GREEN down regulated
- Left side correlation with VAS score for all 6 cASL maps
- Highest correlation reveals a gene BMX involved in regulation of IL6 in pts with RA

Research

Clinical, imaging and genetic characterisation of Cluster headache

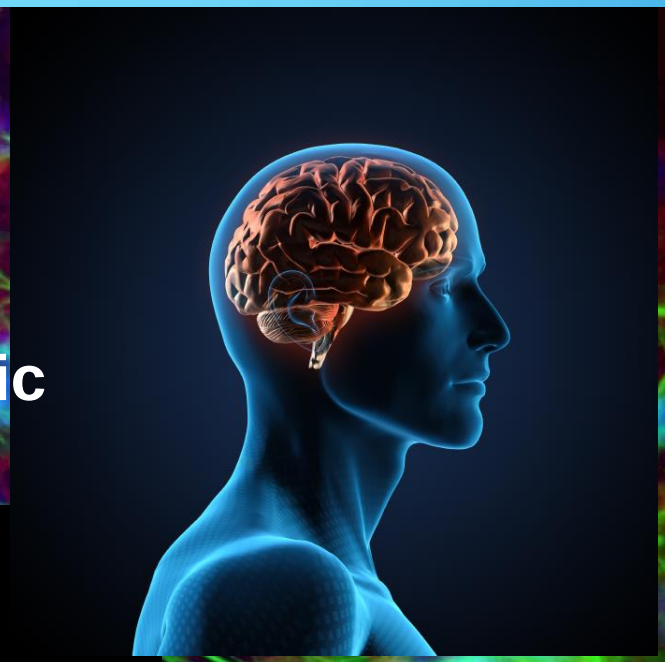
- Dr Norazah Bakar PhD St
- Prof Manjit Matharu UCL
- Mat Howard IoP KCl
- Steve Williams IoP KC
- Dr Sam Chong KCH

Trigeminal autonomic cephalgias
Cluster headaches
SUNCT and SUNA

Post traumatic neuropathy (lecture 3)

TRIGEMINAL NERVE FOUNDATION
Orofacial pain website

’to provide excellence in education, management and prevention of trigeminal chronic orofacial pain’



THANK YOU