Pain or pleasure?

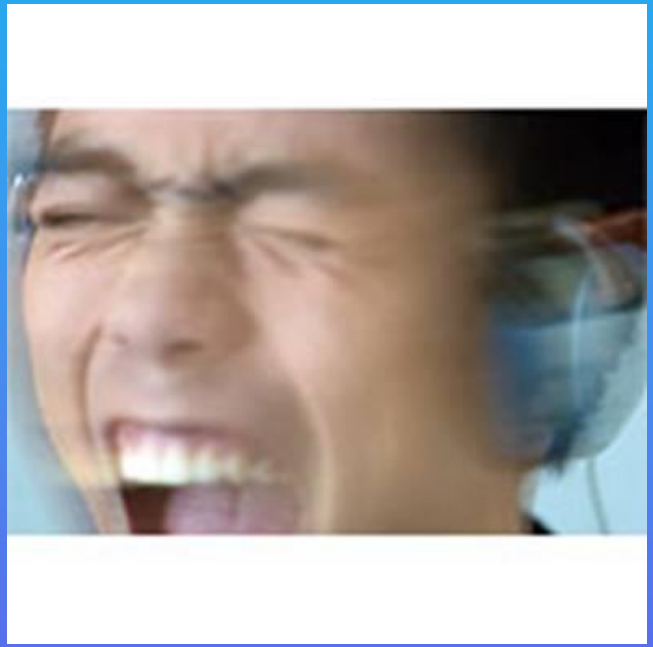
Tara.Renton@kcl.ac.uk

KING'S College LONDON

University of London

An update

- What is pain?
- What causes pain?
- How do we feel it?
- What influences perception of pain?
- Assessment of pain



Consequences of pain

Side effects are a major hurdle in treating chronic pain, which costs the United States around $100 billion annually in treatment and lost wages.

About 50 million adults in the United States suffer from chronic or persistent pain, according to an article on the subject in the journal Science.

Accounts for more than 20 percent of doctor's visits and 10 percent of the trillions of dollars spent on health care.

What is pain?

- Organic / psychological cause
- Subjective experience
  - Sensation
  - Nociception with physical and psychological effects
- Individual response
  - Suffering
  - Behaviour
  - age / gender / experience / personality / anxiety settings / trust in clinician / stress
- Invisible to others

- Definition of pain

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"

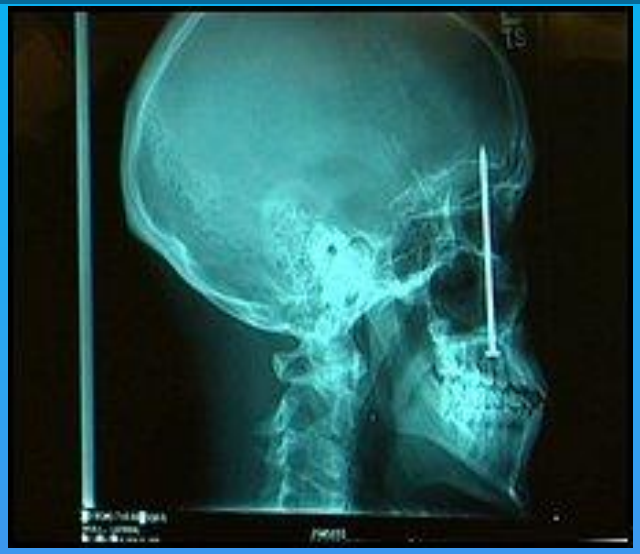
(IASP, 1979)

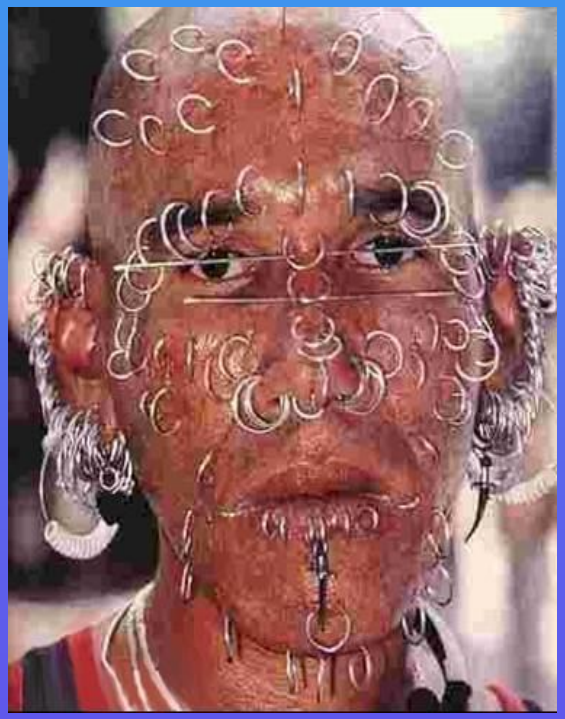
Pain - Acute

‘Healthy pain’ due to inflammation

Infection / autoimmune / trauma

thermal / mechanical / chemical





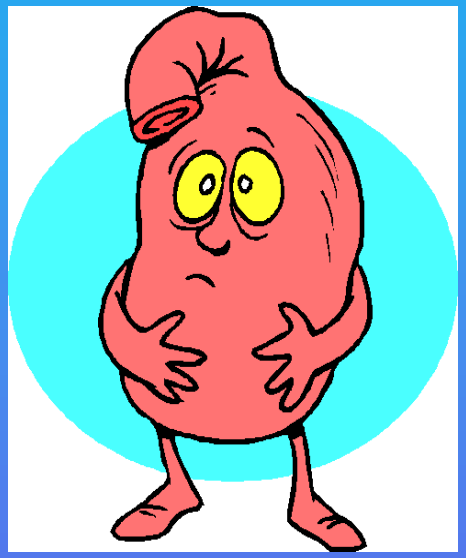
Chronic Pain

Unhealthy / Neuropathic pain lasting > 3 months

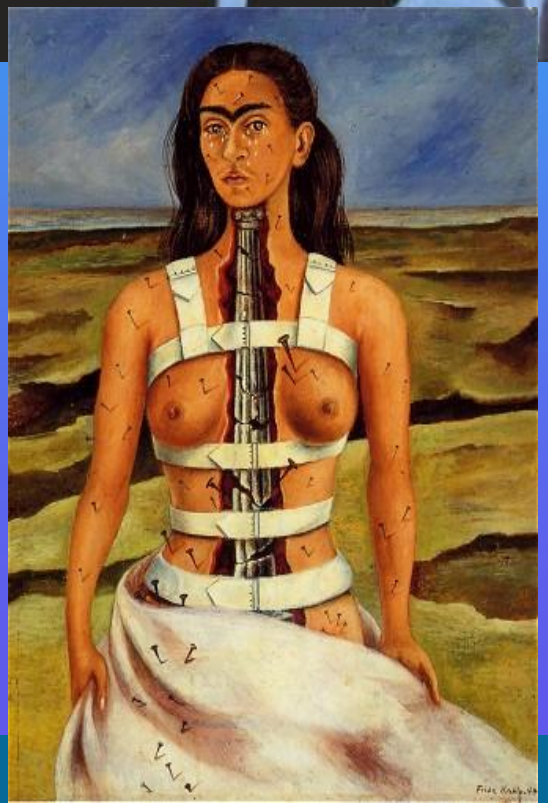
Back pain 47.5%

Head ache 45.2%

Joints 41.7%



Disease of the neuromatrix



Chronic pain

neuropathic or nerve pain

Diabetic burning foot
Post herpetic neuralgia
HIV neuropathy
Chemotherapy
MS
Post surgical neuralgia

Breast surgery 25% Knee surgery 35% Herniorraphy 40%
Thoracotomy 40% Limb amputation 20-60% Third molar surgery?

Chronic pain consequences

33% of US population suffer
13% work force is compromised
USA $61.4 billion dollars/year lost on
Diabetic and HIV neuropathy
Accounts for £40 million GNP / year UK

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

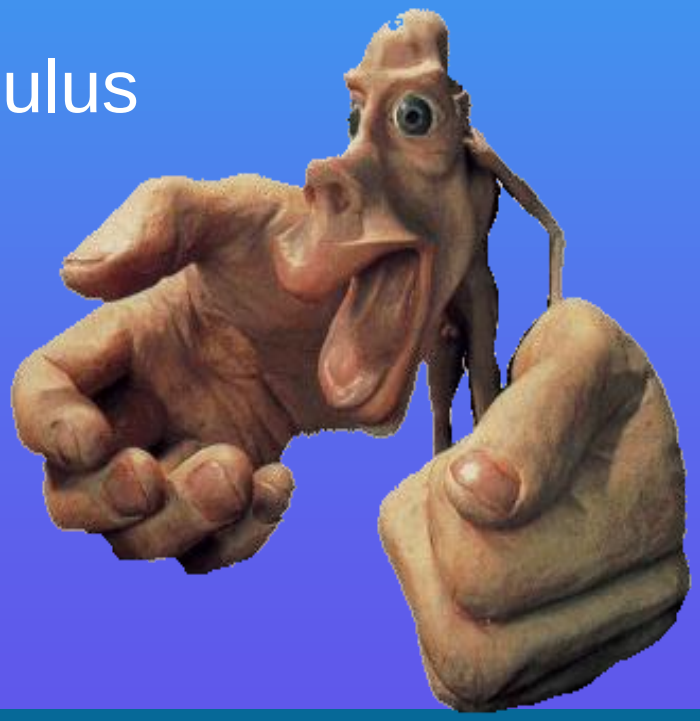
- Somatosensory cortex changes

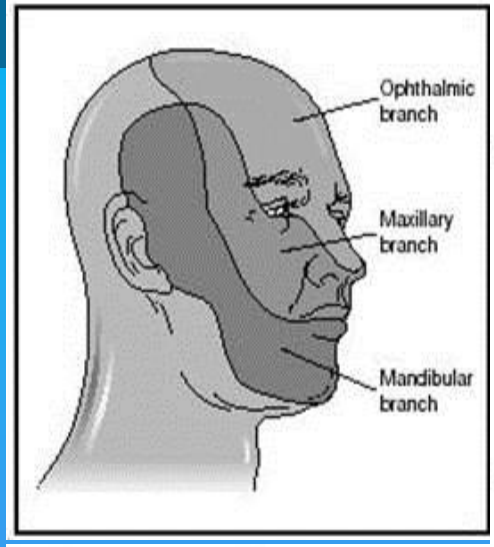
Genetic predisposition

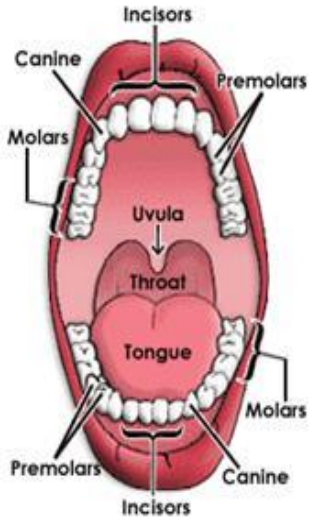
Trigeminal nerve

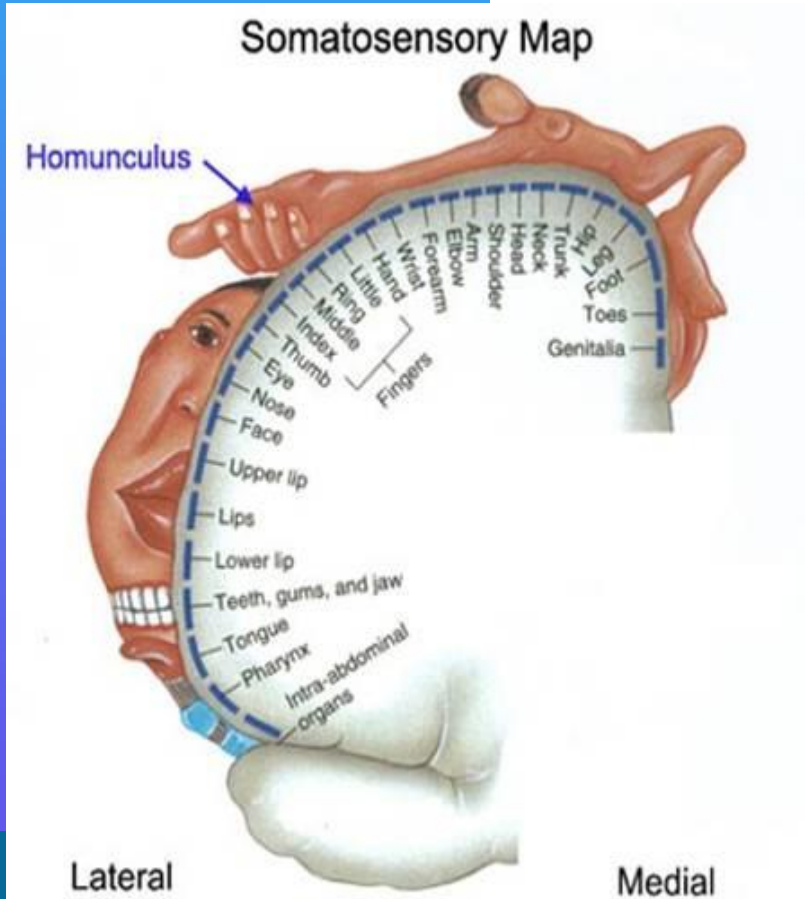
Sensory supply to face, scalp and mouth

Homunculus









Trigeminal nerve pain

- Education
- Complex region
- Consequences
  - Social function
  - Eating
  - Drinking
  - Speaking
  - Kissing
  - Make up / shaving
  - Sleeping

Classification of Chronic orofacial pain

Trigeminal chronic pain

Neurovascular	Neuropathic	Idiopathic
Tension HA	Trigeminal N	Burning Mouth S
Migraine	Typical / atypical	TMJ pain
Cluster HA	PHN	Persistent idiopathic
Giant cell arteritis	Glosspharyngeal N	(ATFP / ATO)
SUNCT	Post surgical N	
	Lingual inferior alveolar nerve injuries	

Neurovascular

- Exclude sinister headaches 1%
  - >50 yrs Tumour 1%
  - Subarachnoid haemorrhage - recent trauma LoC
- Migraine 10-17%

  Five or more lifetime headache attacks lasting 4-72 hours each and symptom-free between attacks

  moderate to sever pain, unilateral +/- aura visual signs
- Cluster headaches 5% - SUNCT

  Male:female ratio 4:1 to 20:1 / 30yrs +

  Severe episodic pain lasting 15-180 minutes

  Unilateral Orbital, supraorbital or temporal

  8x a day to every other day for a period of 2 -12 weeks
- Tensions type headaches

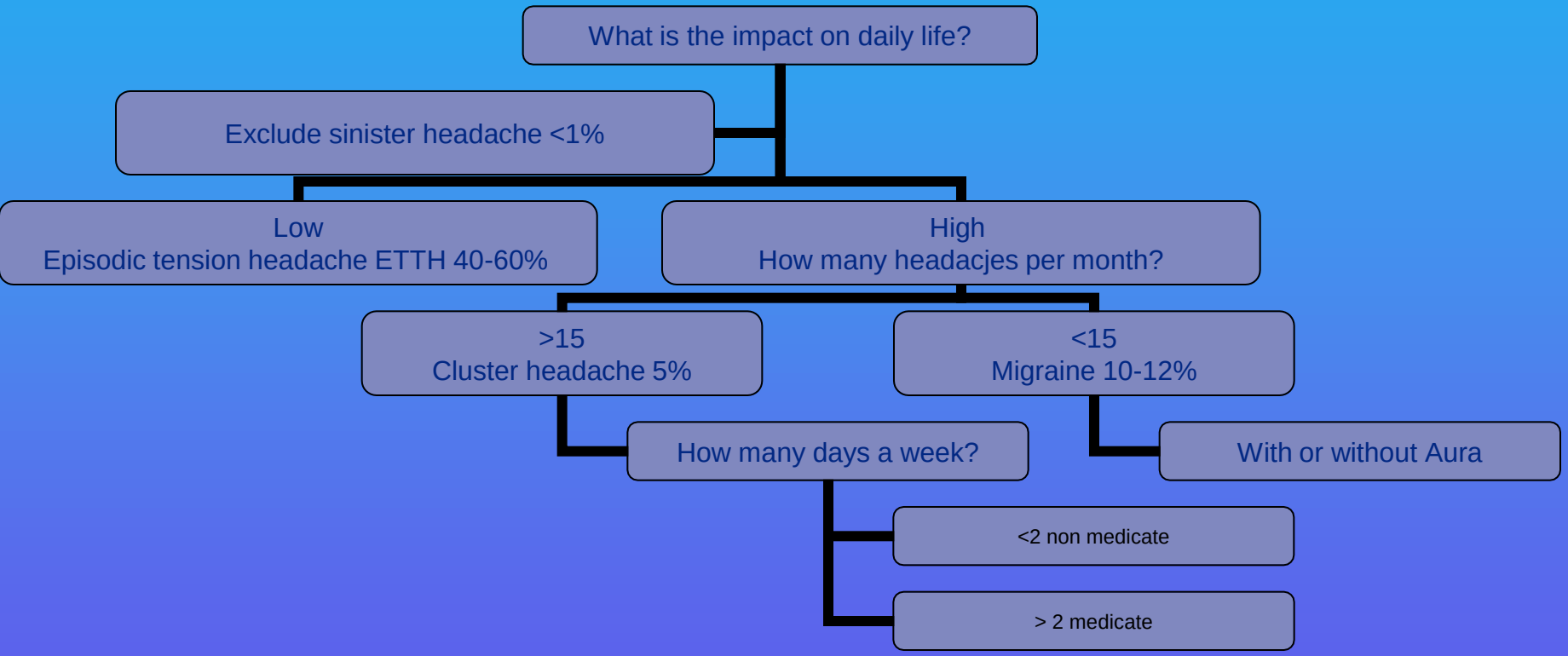
  30-78% population -Highest socioeconomic impact

  At least 10 episodes occurring <1 day a month on average

  Infrequent episodes lasting from 30 minutes to 7 days

  Typically bilateral
- Medication over use headaches ***30-78%***

MIPCA


What is the impact on daily life?
Exclude sinister headache <1%
Low
Episodic tension headache ETTH 40-60%
High
How many headacjes per month?
>15
Cluster headache 5%
<15
Migraine 10-12%
How many days a week?
With or without Aura
<2 non medicate
> 2 medicate

Neuropathic with ‘neuralgia’

- Trigeminal neuralgia (TN)
  - Typical
  - Atypical
- Post herpetic neuralgia (PHN)
  - > 50 yrs 60% likely to develop pain post shingles
  - Ramsay Hunt syndrome
- Glossopharyngeal neuralgia
  - Acute pain pharynx, tongue base, mastoid regions
- Post traumatic V neuralgia
  - Lingual nerve injuries
  - Inferior alveolar nerve

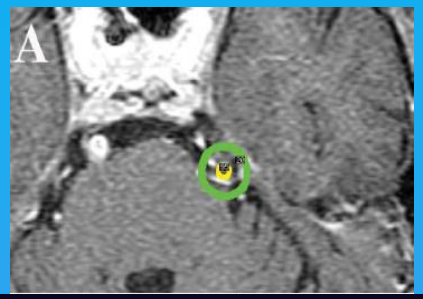
BMS?

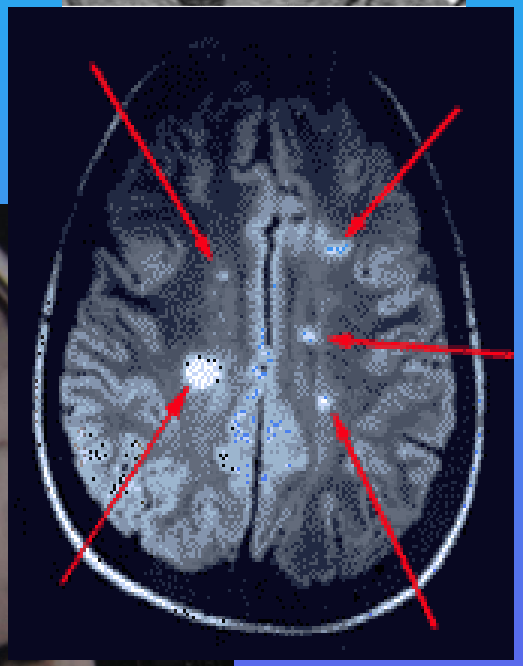
V neuralgia seen in patients with

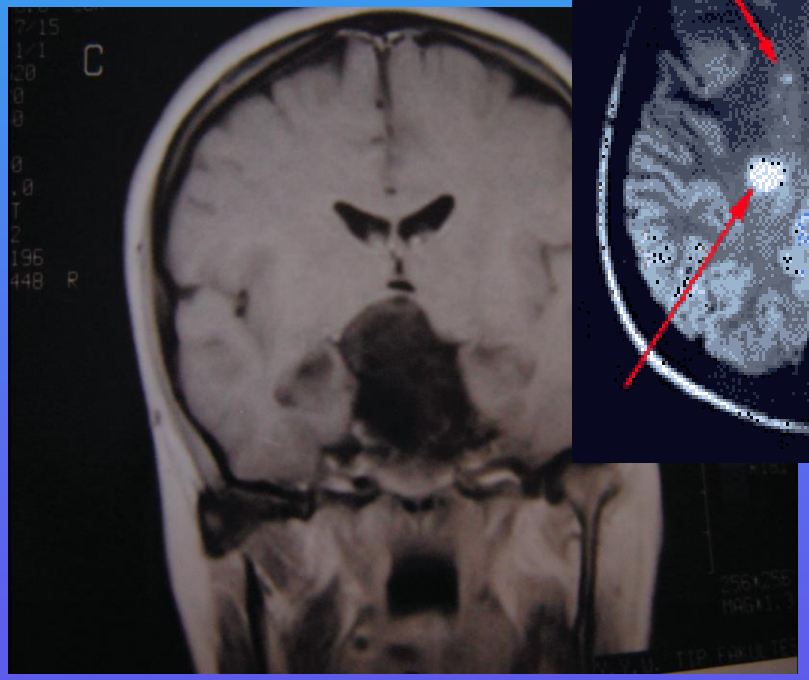
Diabetes
HIV
Chemotherapy
MS

Exlude central pathology

- Classical TN
  - vascular compression
- Multiple sclerosis
  - MRI plaques
- Stroke
- Vasculitis
- Post herpetic neuralgia
- Tumours
  - Meningioma

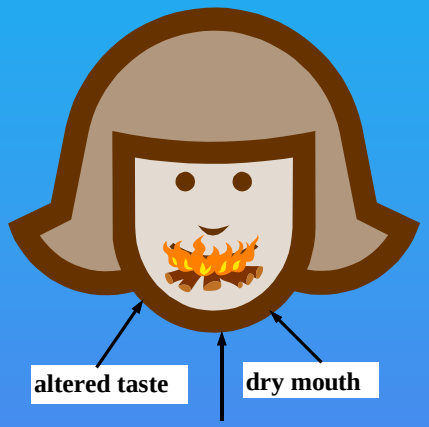


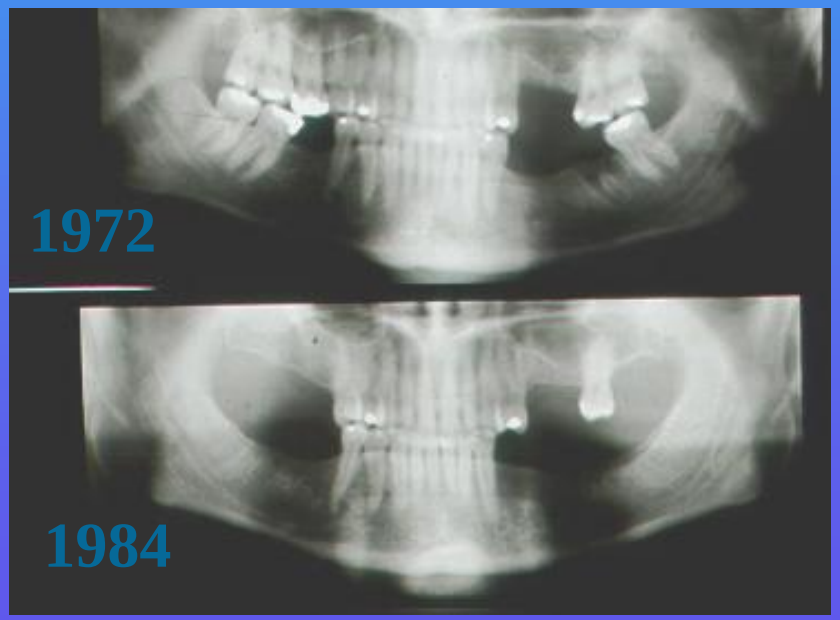




Idiopathic chronic OFP

- TMJ pain
  - Functional - chewing gum
  - Arthritides
  - Derangement
- BMS
  - ? neuropathy
- Persistent idiopathic
  - Extraoral / facial
  - Intraoral / odontalgia





Patients in pain

How do we feel the "ouch“?

Pain Process

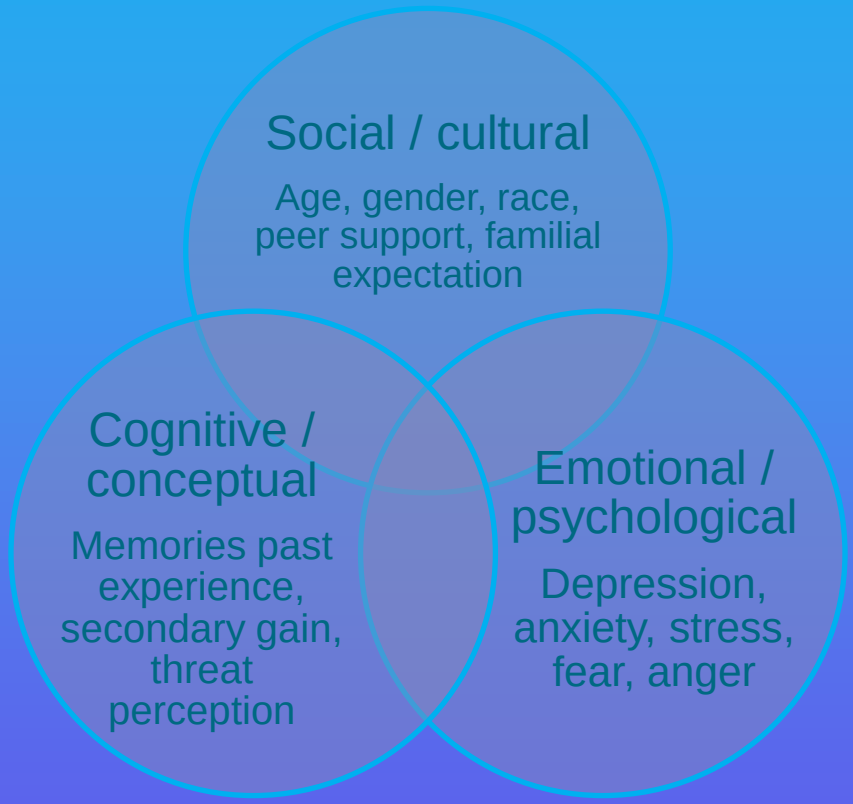
Nociception

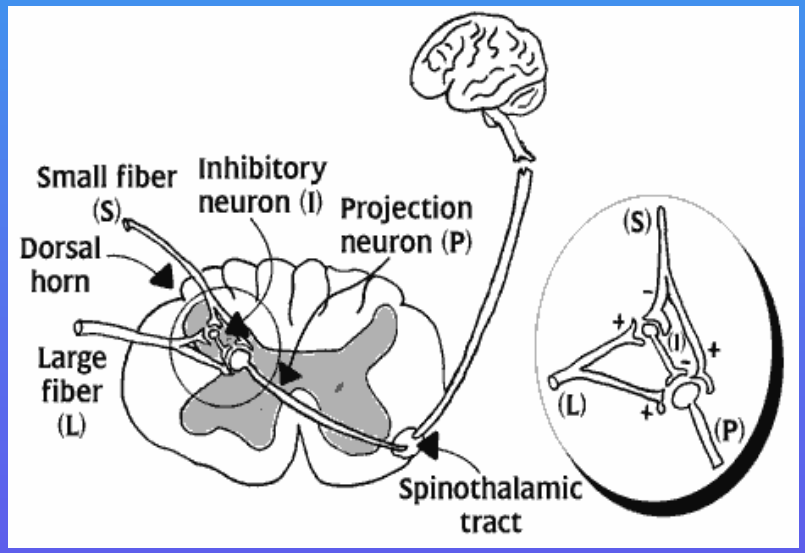
Sensation

Behaviour

Suffering

Bio psycho social Model





Descartes 1650 in Stockholm

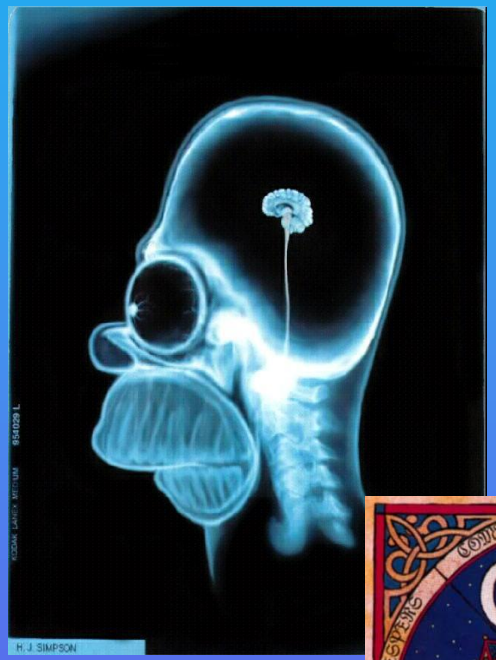
Canadian psychologist Ronald Melzak and British physiologist Patrick Wall 1965

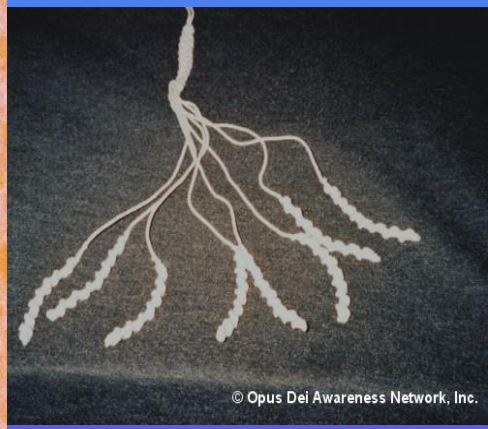
Perception of pain

Perception of pain

‘I enjoy the pain’

David Beckham on tattoos





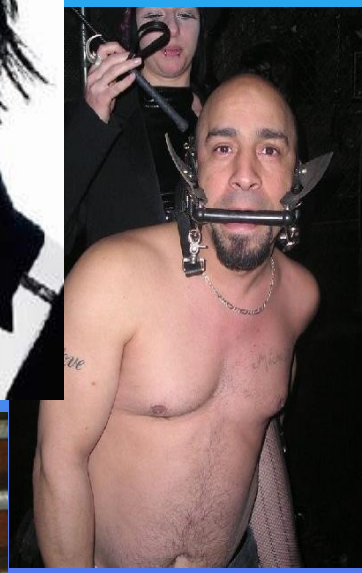
Opus Dei Priest ‘Pain is good’

Pleasure and Pain

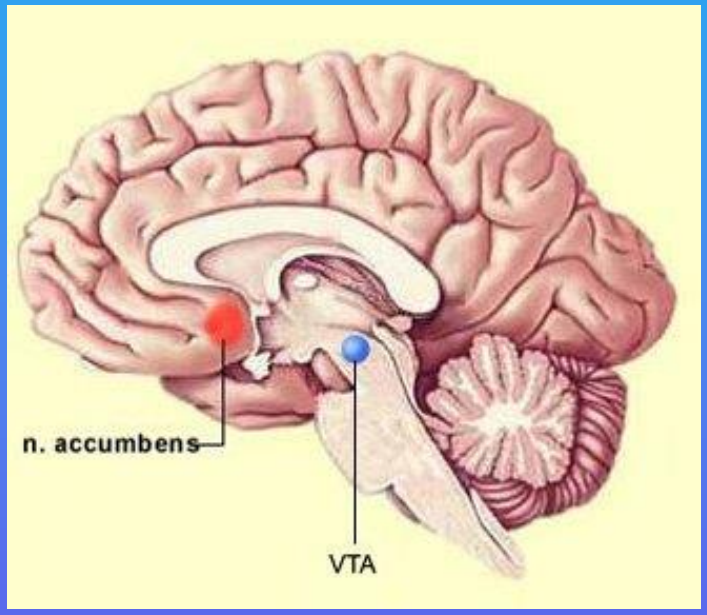
Brain images focused on areas experience of pain and on areas activated by cocaine, food and money.

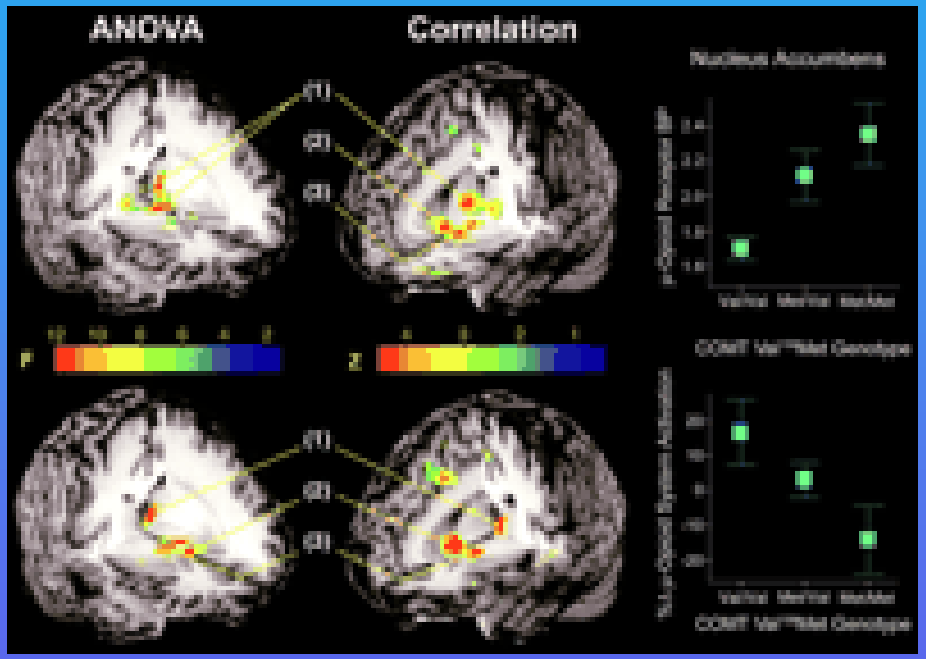
Painful 'hot' temperatures activate the reward-associated structures, particularly in an area called the nucleus accumbens

Dissociation and self harming



Nucleus accumbens





The COMT protein is a sort of brain janitor, "cleaning up" the spaces between brain cells after chemicals called neurotransmitters finish sending signals between brain cells. Specifically, COMT metabolizes, or breaks down, the brain chemicals called dopamine and noradrenaline, also known as norepinephrine.

Those with two copies of the val form of the gene make only powerful COMT that mops up dopamine rapidly. People with two copies of the met form of the gene make only poor COMT, and can't "clean up" the dopamine in their brains very well. Those with one copy of each gene variety -- the majority of people -- make some of each kind of COMT, yielding a "normal" dopamine-metabolizing system.

Dopamine is often known as the brain's "pleasure chemical", because of its role in transmitting signals related to pleasurable experiences.

But it also has a more general role, together with noradrenaline, in how we respond to many kinds of stimuli that are "salient", or relevant to our lives. And animal studies have shown that when the dopamine system is highly active, the brain reduces its production of other chemicals: the endogenous opioids, or so-called enkephalins.

Enkephalins, and their related chemicals called endorphins, are part of the brain's own painkiller and stress-response system. They regulate and suppress painful or stress-related signals in the brain by binding to proteins on brain cells called mu-opioid receptors.

Natural endorphins aren't the only thing that can bind to these receptors and kill pain; so can painkiller medications such as morphine, some anesthetics, and illegal drugs such as heroin. No matter what's binding to the receptors, the effect is typically a quelling of pain and our responses to it.

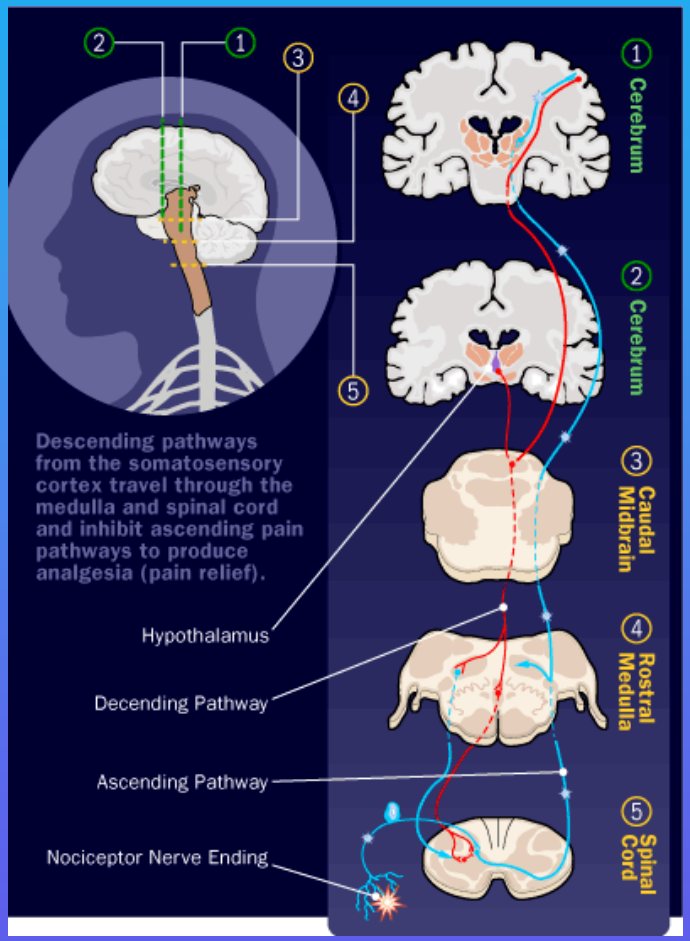
The differences between met/met and val/val participants in the activation of the mu-opioid system were most significant in the cingulate cortex, anterior thalamus, the thalamic pulvinar, and the basal ganglia, including the nucleus accumbens and ventral pallidum, and the amygdala. These are areas of the brain that are involved in our response to painful and emotionally important stimuli. They all help integrate multiple aspects of those experiences, to promote particular patterns of response.

The new results build on what Zubieta and his colleagues have previously shown through their studies of the mu-opioid system and pain response.

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



Peripheral

Acute inflammatory pain

Tissue injury

Cell damage

- Trauma mechanical, chemical . Radiation. heat

Cytokine release

- Attract immune cells
- Nerve activation via receptors via **NGF**

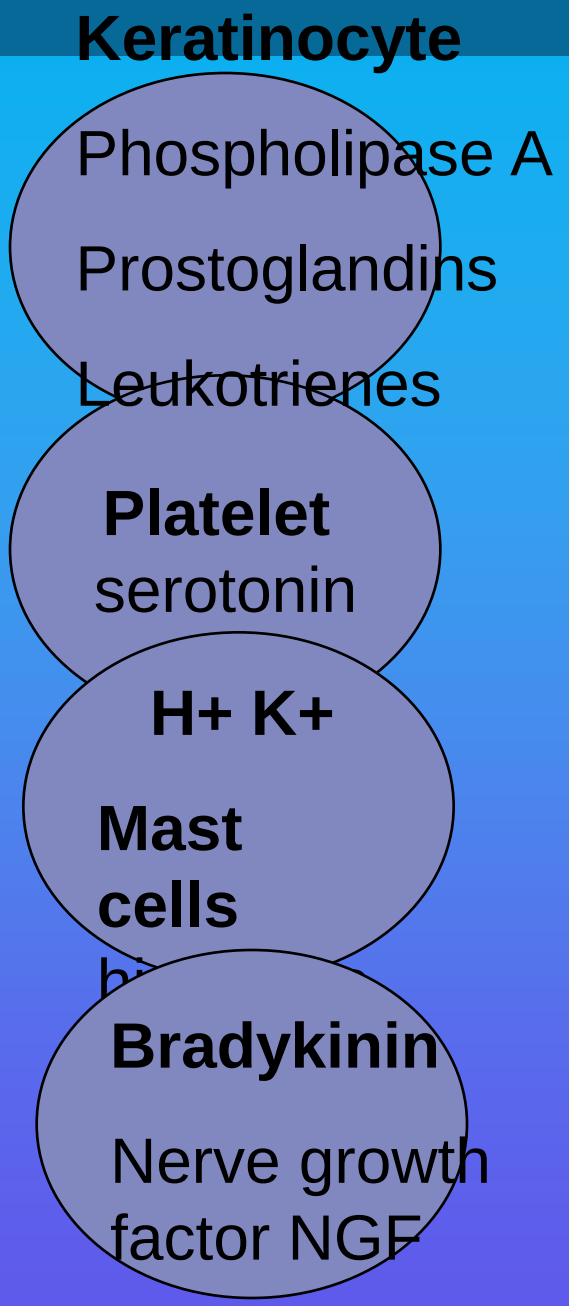
Neural depolarisation (PNS)

- Action potential
- Signals primary, secondary, tertiary (CNS)
- Cortical activation ‘sensing
- Reaction (motor and sensory

More cytokine release
NEUROINFLAMMATION

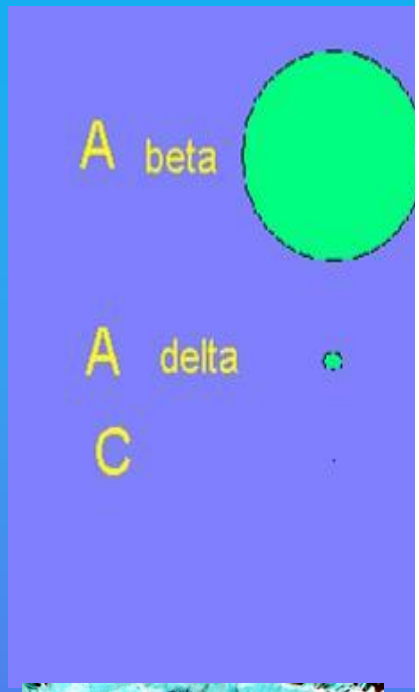
If process prolonged = changes in nervous system

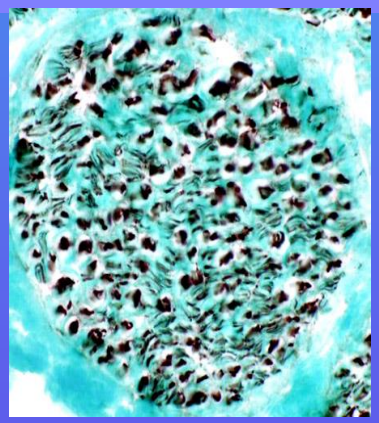
Chronic non inflammatory pain

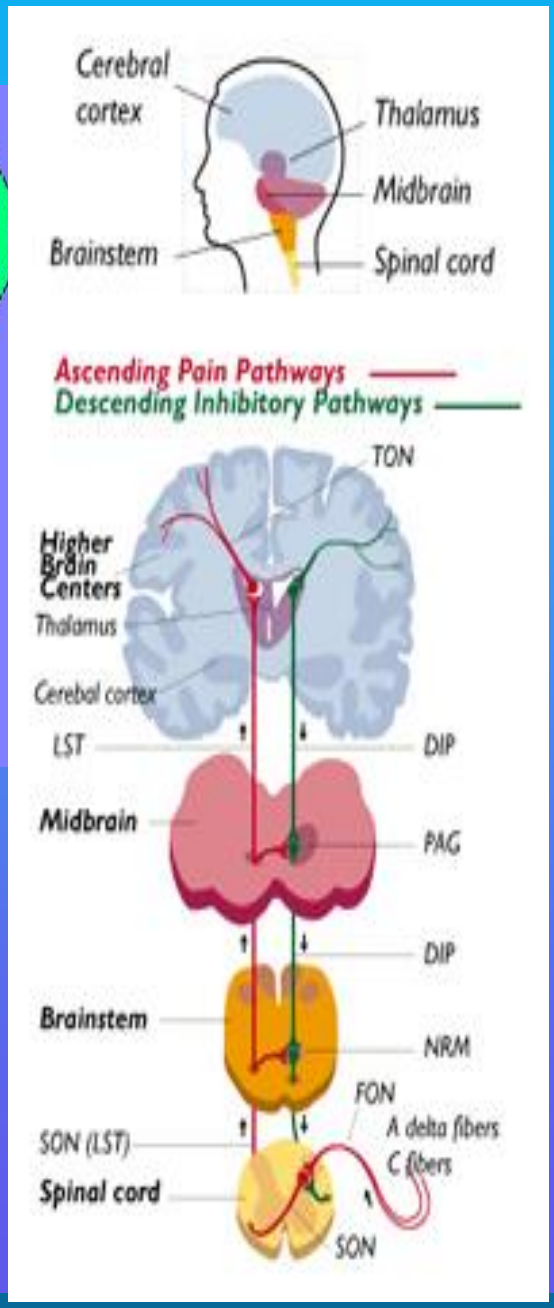


CNS/ PNS interaction

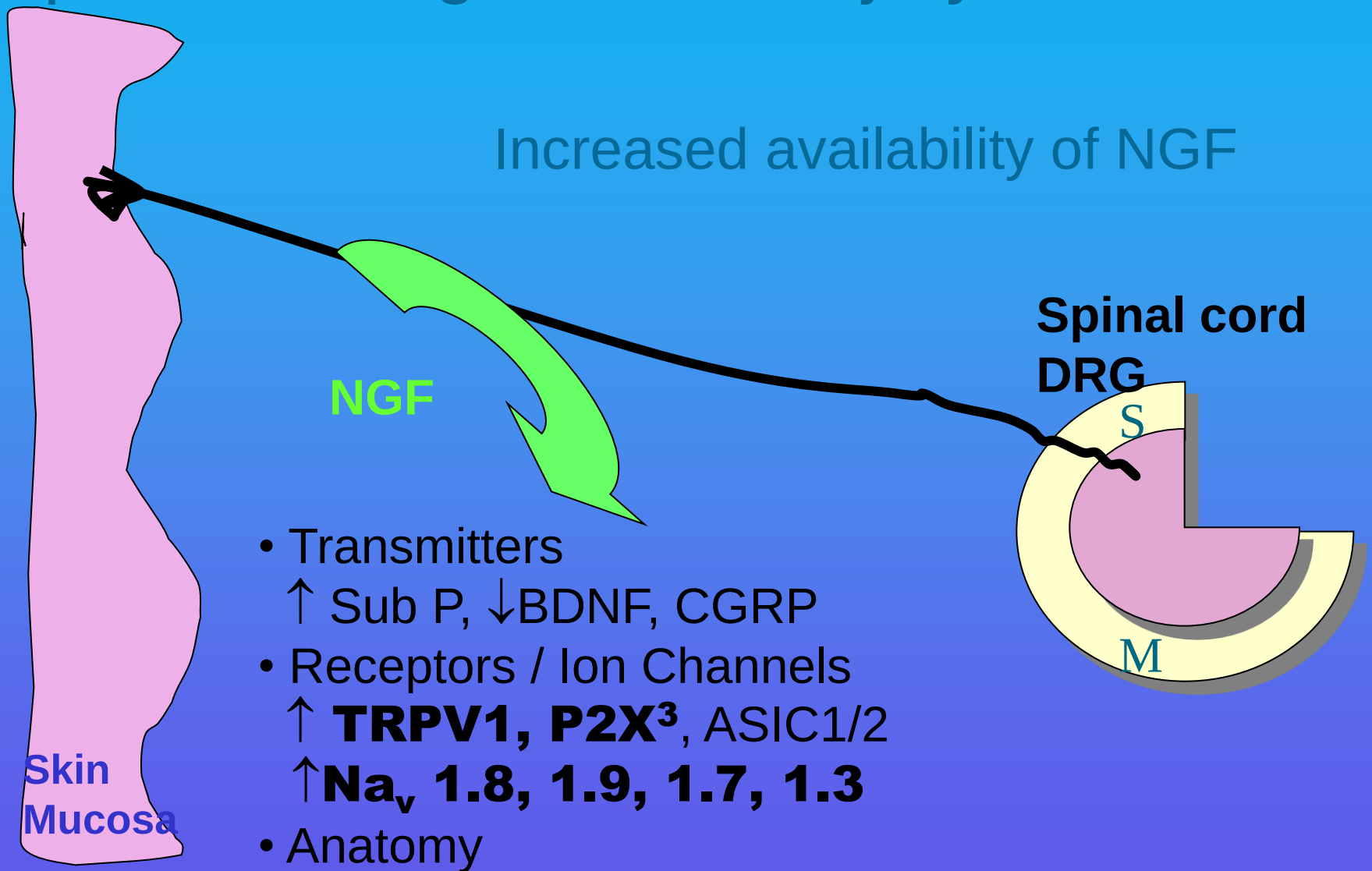
- Receptors
- Primary sensory nerve
  - A Delta and C fibres
- Secondary sensory nerve
  - Lamina I DRG
- Tertiary sensory nerve
  - Specific areas of the brain
    - Thalamus
    - Anterior cingulate cortex
    - S1 / S2
    - Insula
    - Brainstem







Peripheral changes due to injury



- Transmitters
  ↑ Sub P, ↓BDNF, CGRP
- Receptors / Ion Channels
  ↑ **TRPV1, P2X^3**, ASIC1/2
  ↑**Na$_v$ 1.8, 1.9, 1.7, 1.3**
- Anatomy
  ↑GAP 43, innervation density

Specific pain receptors

Transmitters

↓NGF, ↓ SP, ↓ CGRP

Receptors

↓ **TRPV1,** ↓ P2X3

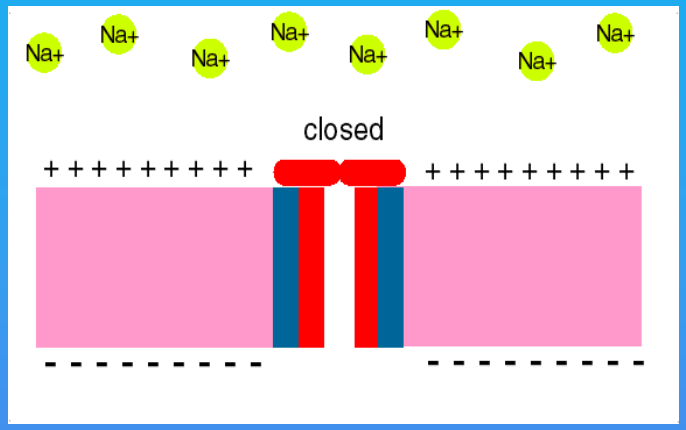
Ion Channels

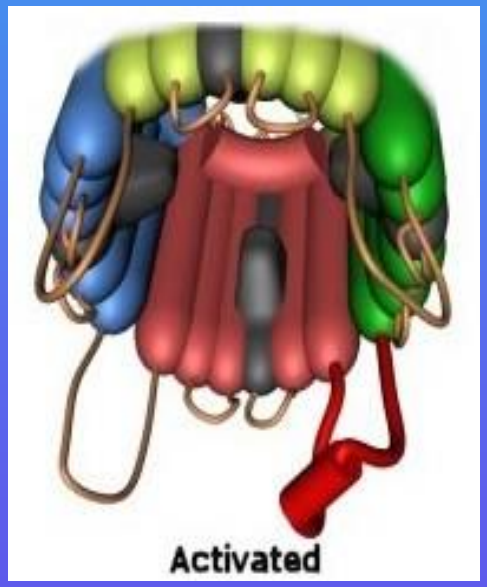
- Na, Ca, K

Anatomy

- degeneration

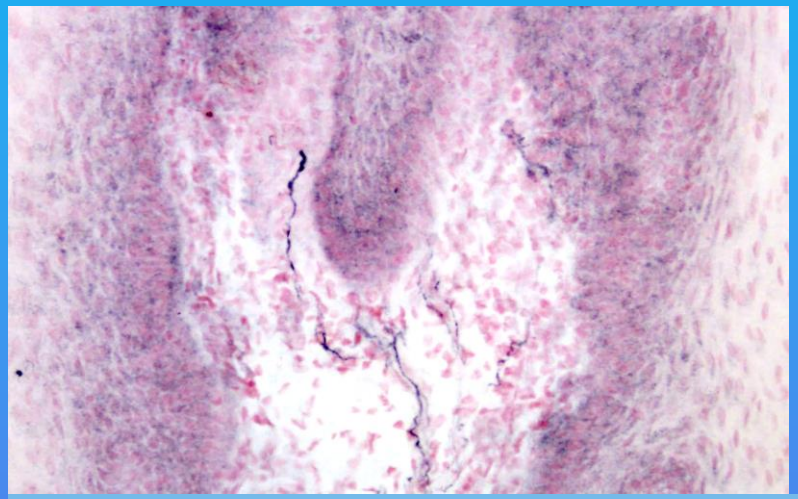
↑ spontaneous activity



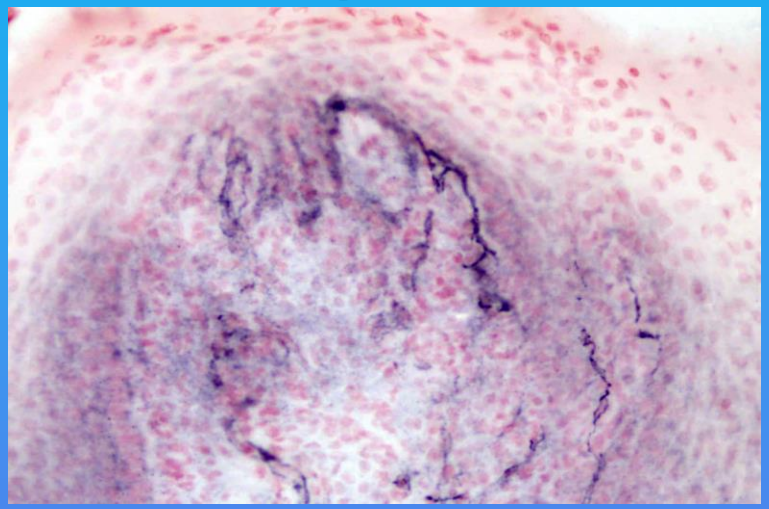


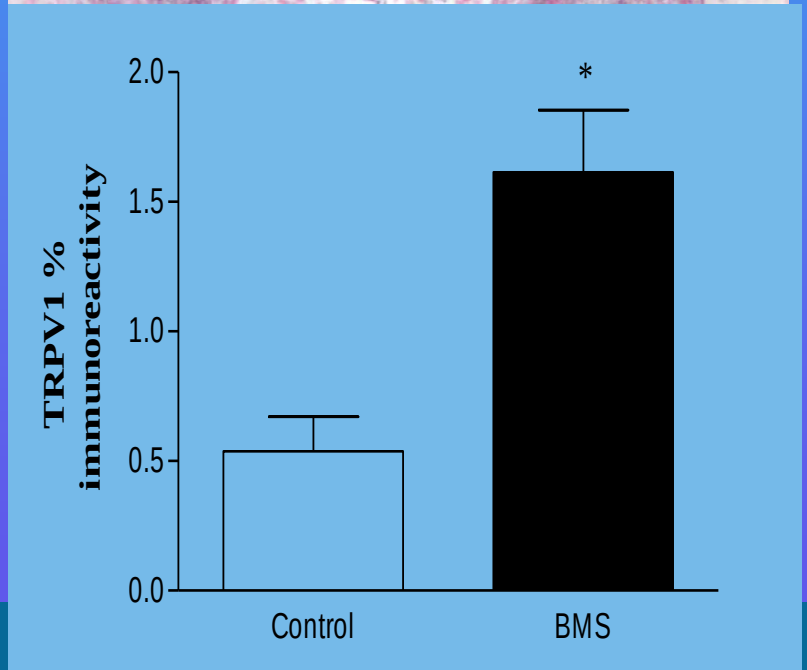
TRPV1 -IR

Control



BMS



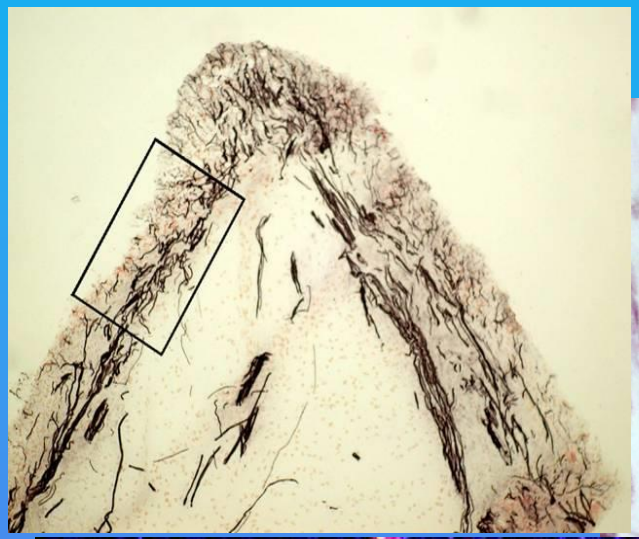


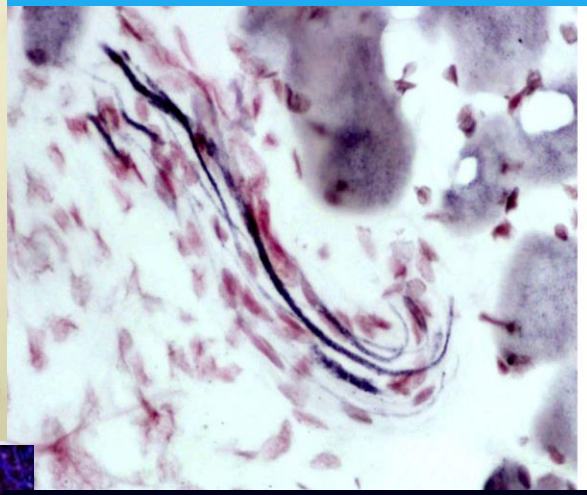
TRPV1 fibres staining in control and in BMS x20.

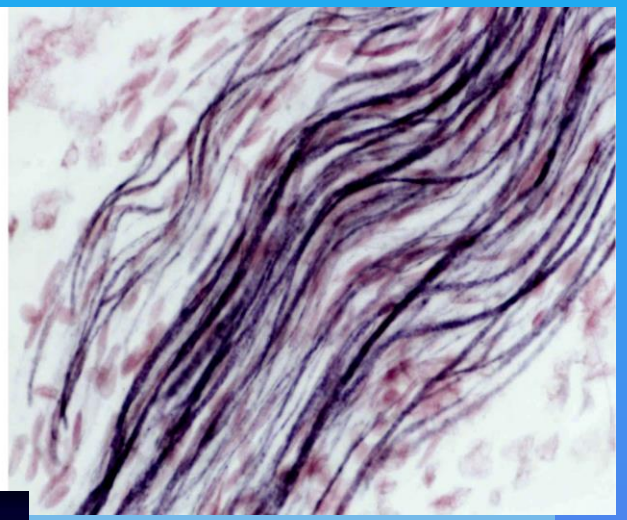
Bar chart shows the mean ± SEM of % area of TRPV1 fibres in control (n=10) and BM (n=10) tongue. * P =0.0011

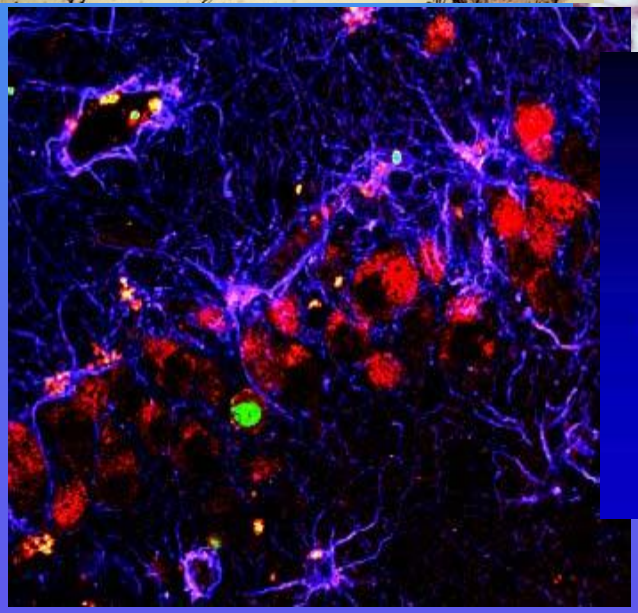
Control

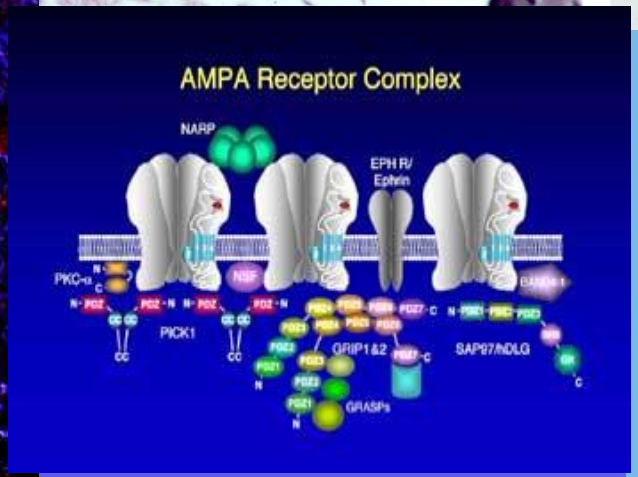
Pain

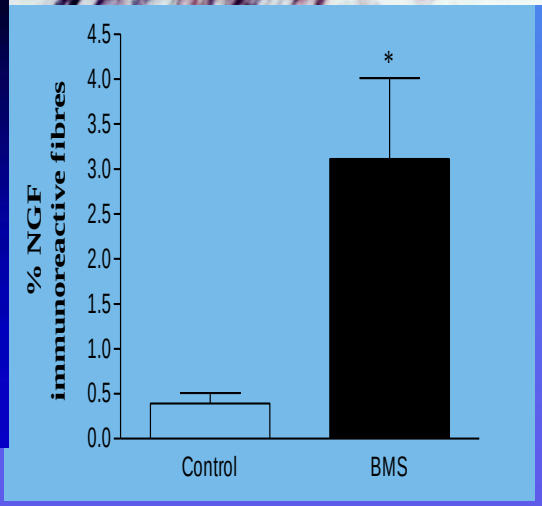






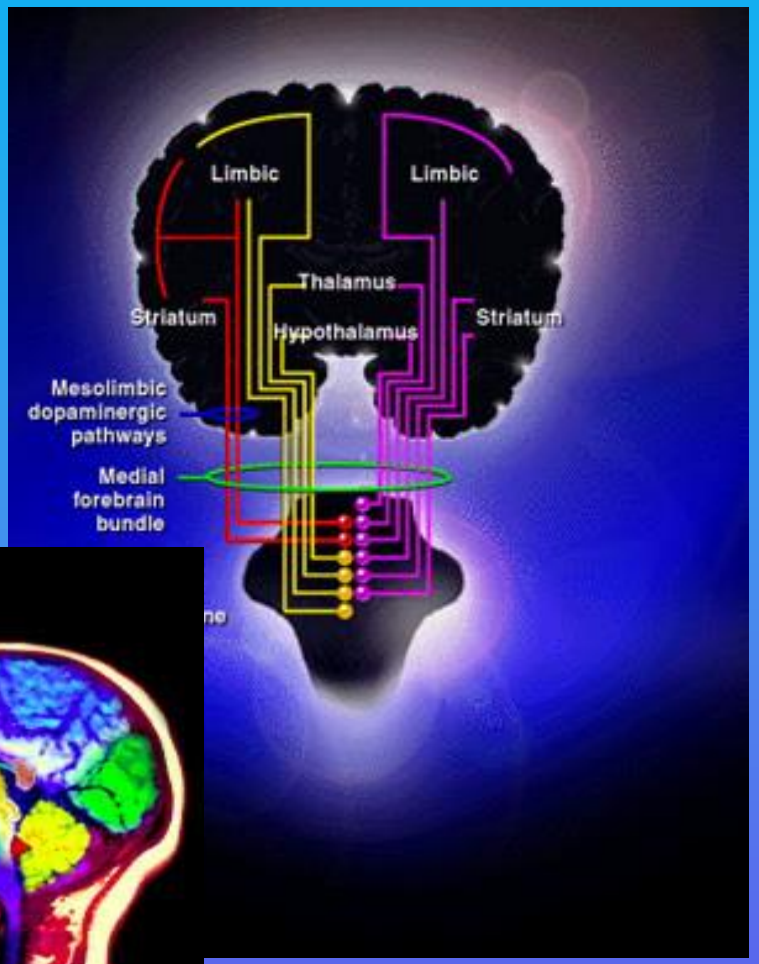


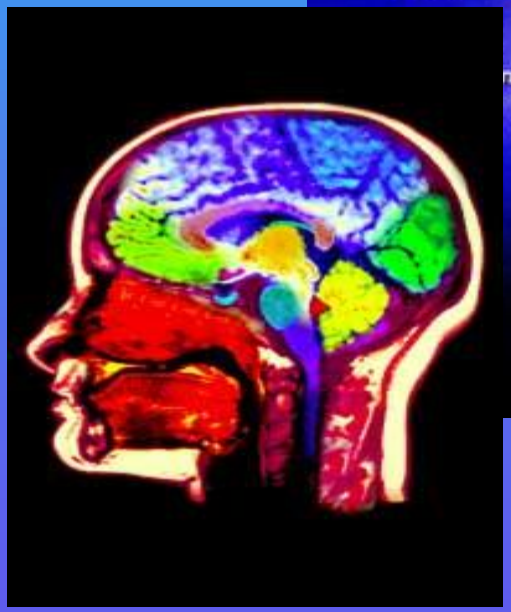




Central neuroanatomy

- 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

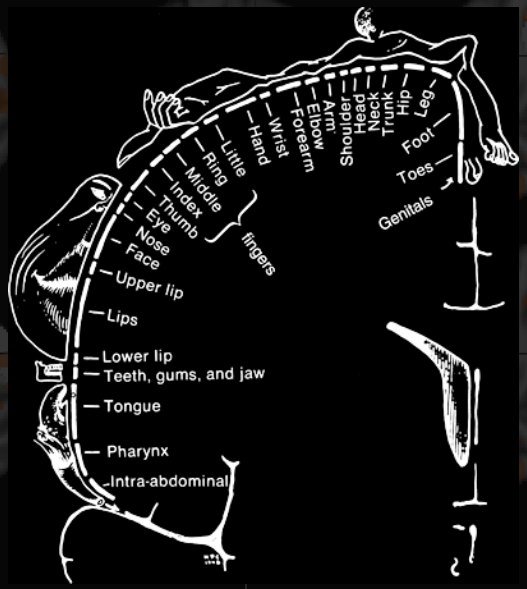




Anatomy revisited

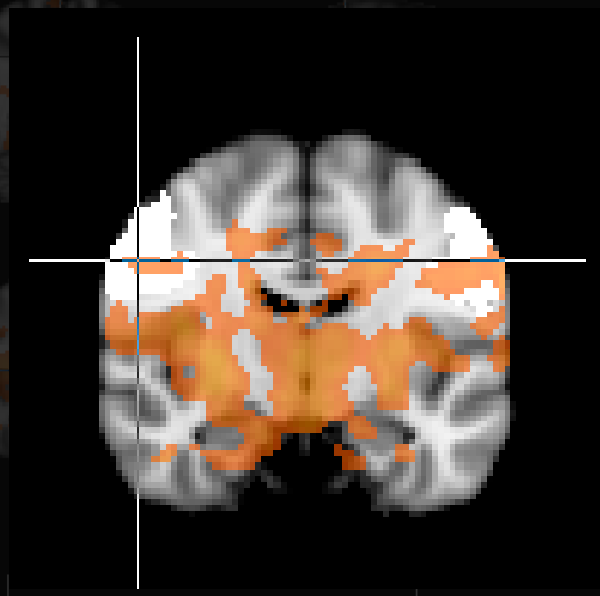
ACC

PCC



S1

S2

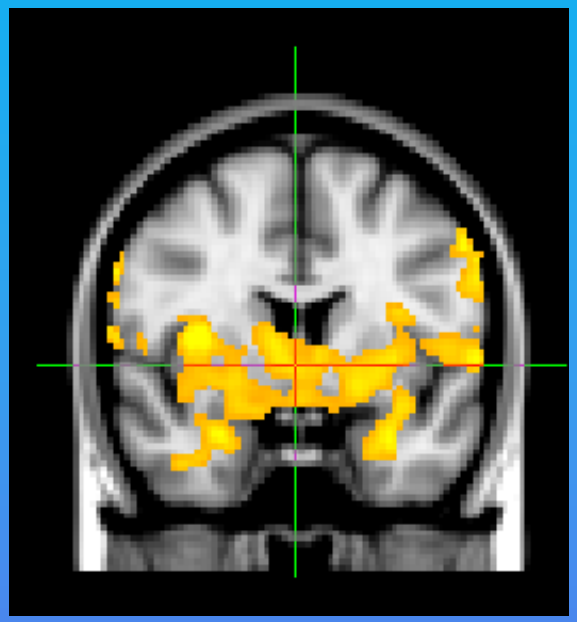


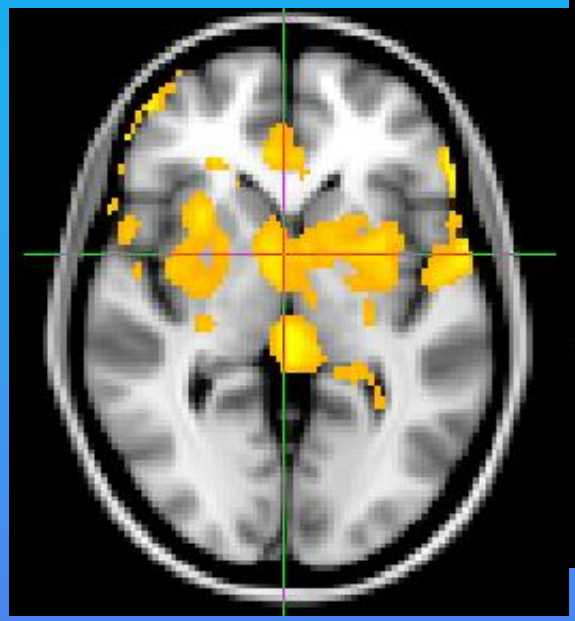
THAL

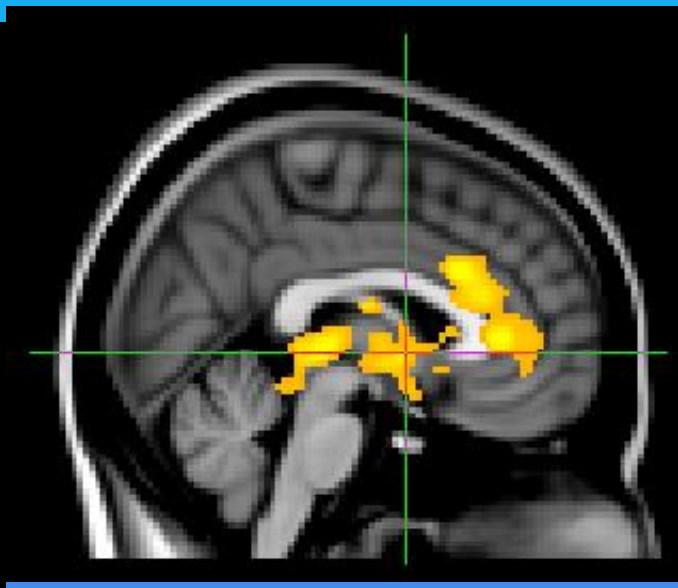
INS

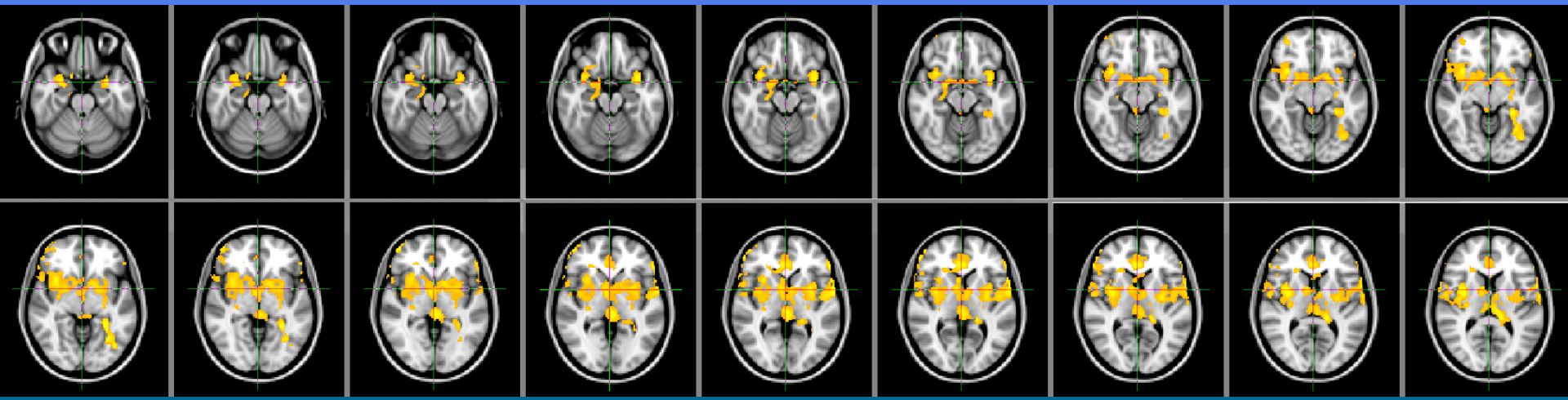
- Additional amygdala, hippocampus, brainstem, and V5 ROIs

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



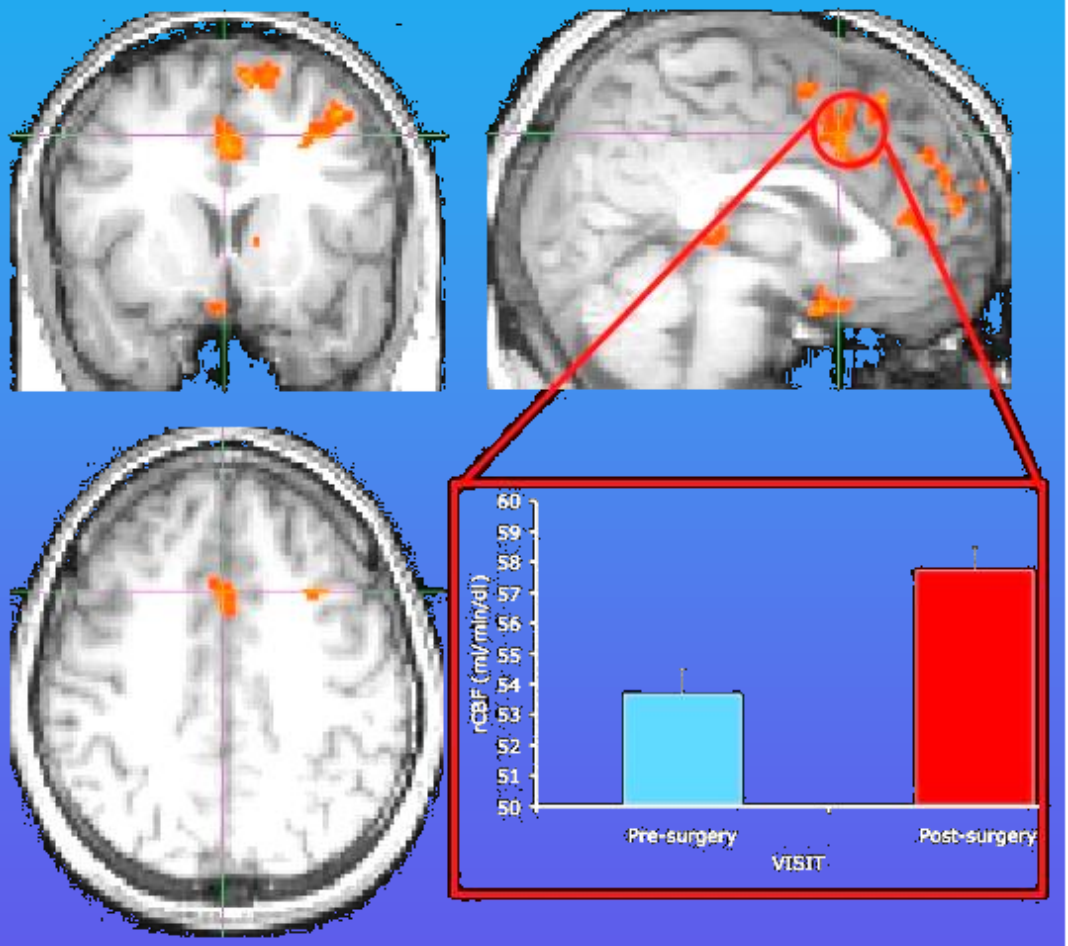




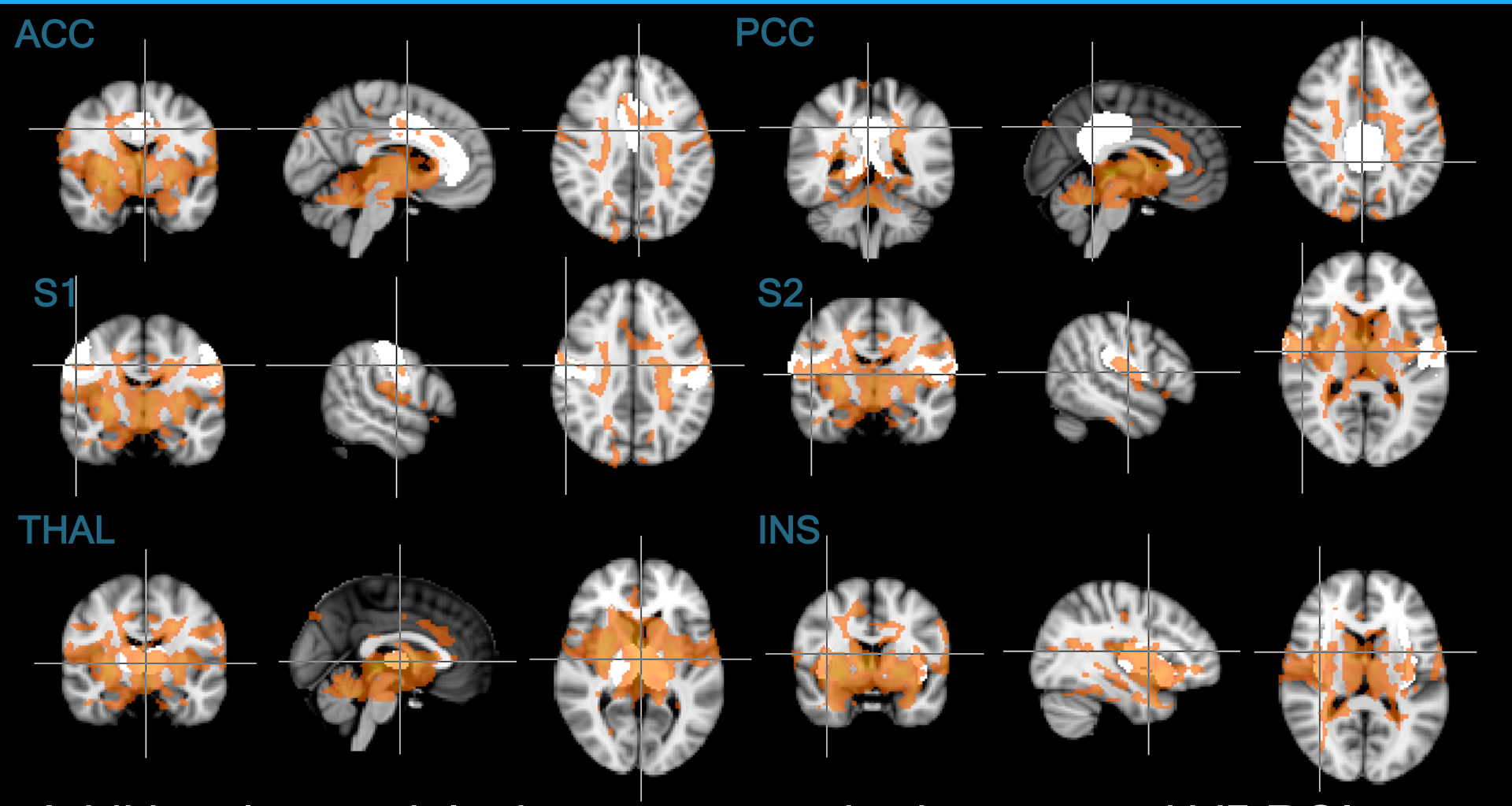


Central pain activity

- 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

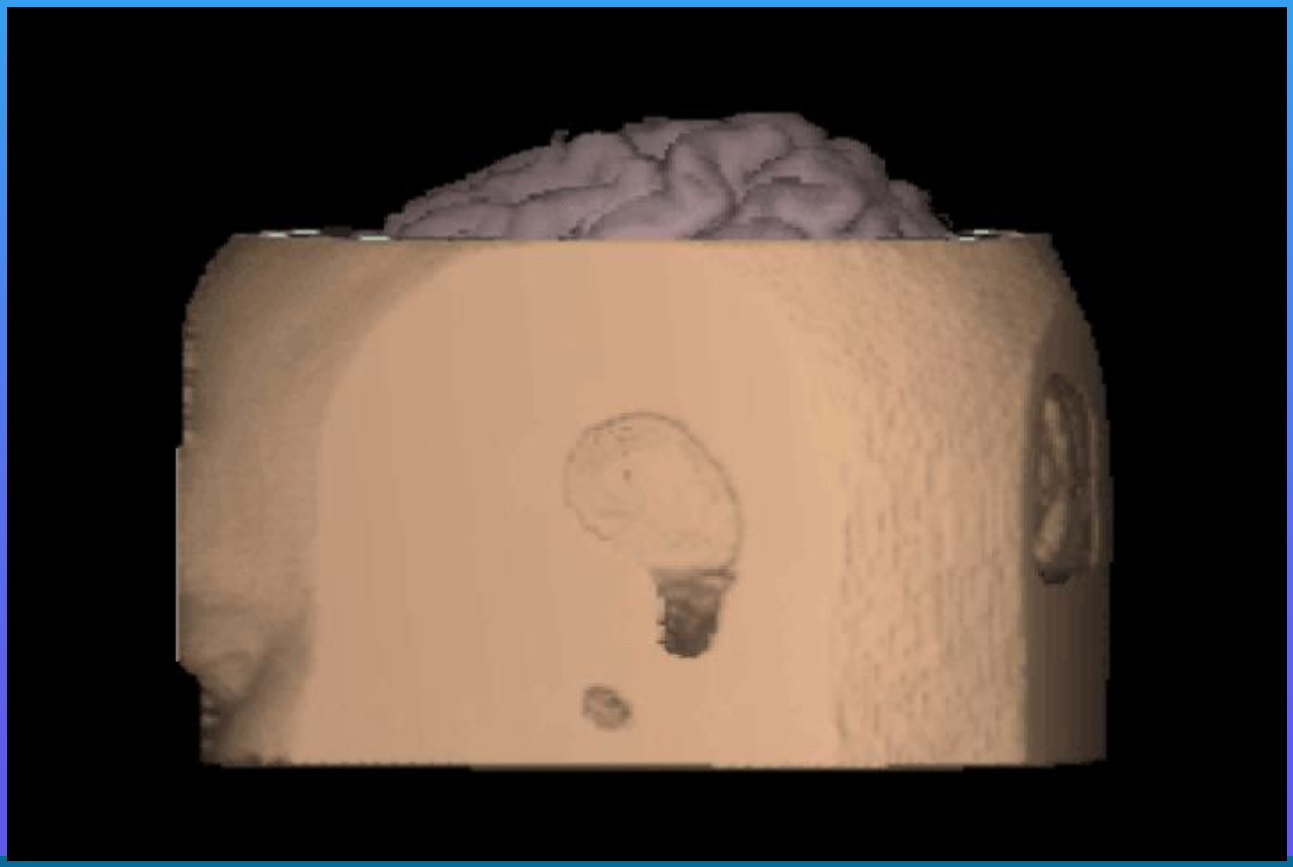


Anatomy revisited

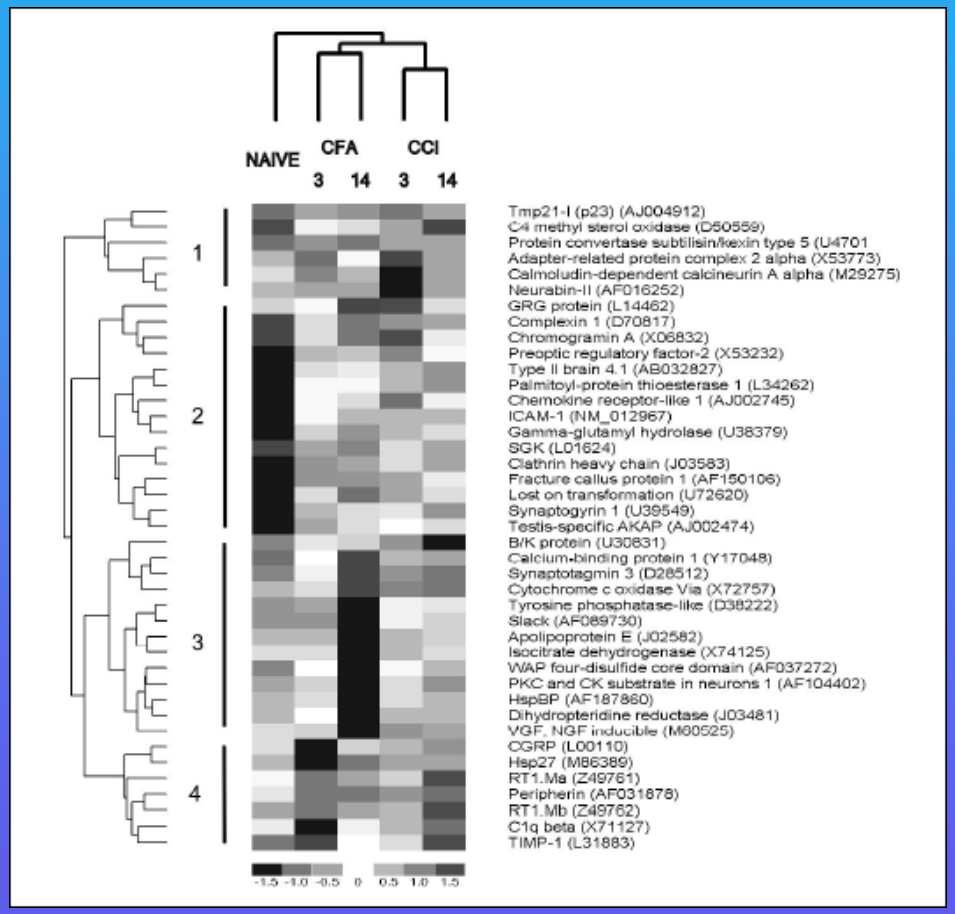


- Additional amygdala, hippocampus, brainstem, and V5 ROIs

Pain in the Brain
fMRI video

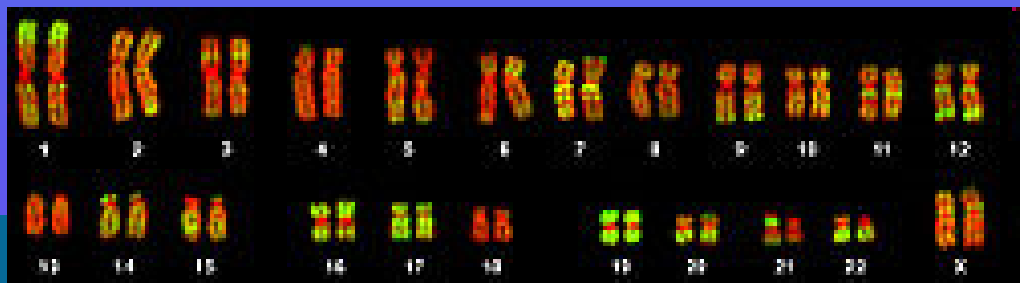


The genetic basis of V pain



The Human Genome

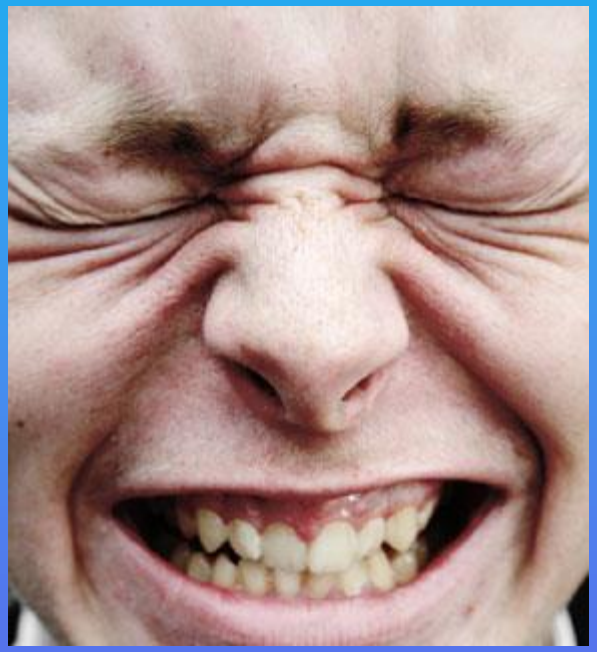
- 3.16 billion base pairs
- 23 pairs of chromosomes
- Human Genome Project has sequenced about 2.8 billion base-pairs to date
- Only 3% of the human genome actually code for proteins
- About 15% of the non-coding DNA in humans is conserved (functional importance)



The genetic basis of V pain

"Human genetics has showed us how the risk of pain is reduced naturally.

GCH1 was the first human gene variant ever associated with the intractable hurt caused by nerve damage.



Nature on 14 December 2006

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

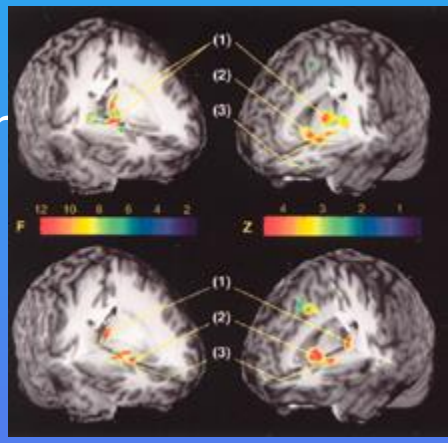
Melanocortin-1 Gene for Red Hair and Pain Tolerance

"It does appear that redheads have a significantly different pain threshold and require less anaesthetic to block out certain pains,"

Muopoid receptor

A small variation in the gene that encodes the enzyme called catechol-O-methyl transferase, (COMT) effect pain tolerance and pain-related emotions and feelings.

The COMT enzyme helps govern aspects of brain chemistry involving the neurotransmitter chemicals dopamine and noradrenaline.



The form of the enzyme containing methionine is much less active in the brain than the one containing valine. Everyone carries two copies of the COMT gene, one inherited from each parent.

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

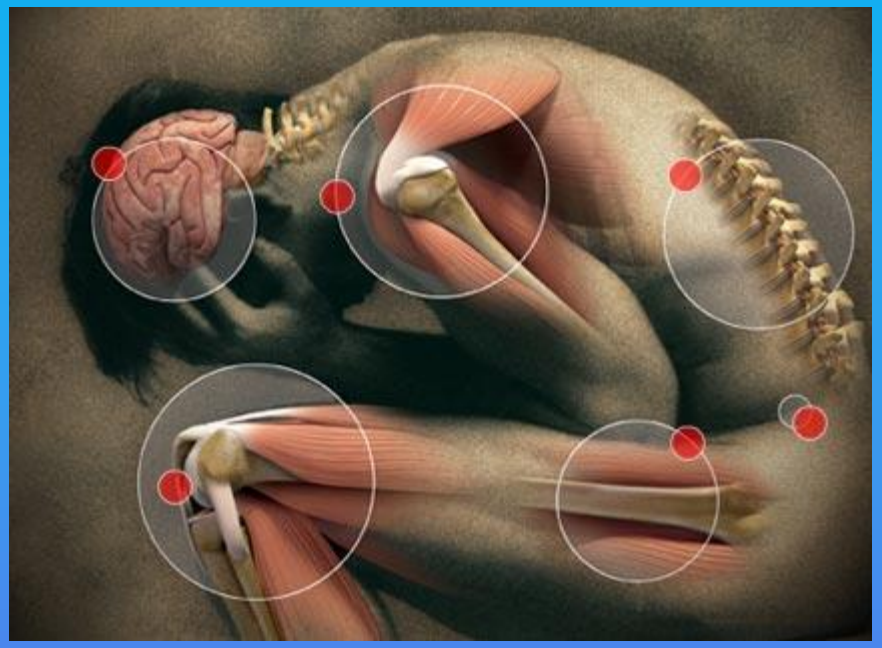
Increased interdisciplinary work (imaging genomics, proteomics, QST) Epigenetics will receive increased attention

Increasing numbers of papers on pain genetics

Assessment of pain

- Pains' multiple components
  - nociception / sensation / suffering / behavior
- Disability
  - lack of mobility, inability to work, difficulty in interpersonal relationships
- Multiple components of pain assessment
  - physical location of pain, description tools
  - functional tools: sickness/impact profile, pain disability index
  - behavioral/cognitive drug use, physician visits
  - economic
  - Socio-cultural, litigation, patient independence, quality of life, family dynamics, patient goals.

Pain assessment



Diagnosis of pain

Pain History

Pain thresholds

Subjective measurement of pain

Indirect measurement of pain

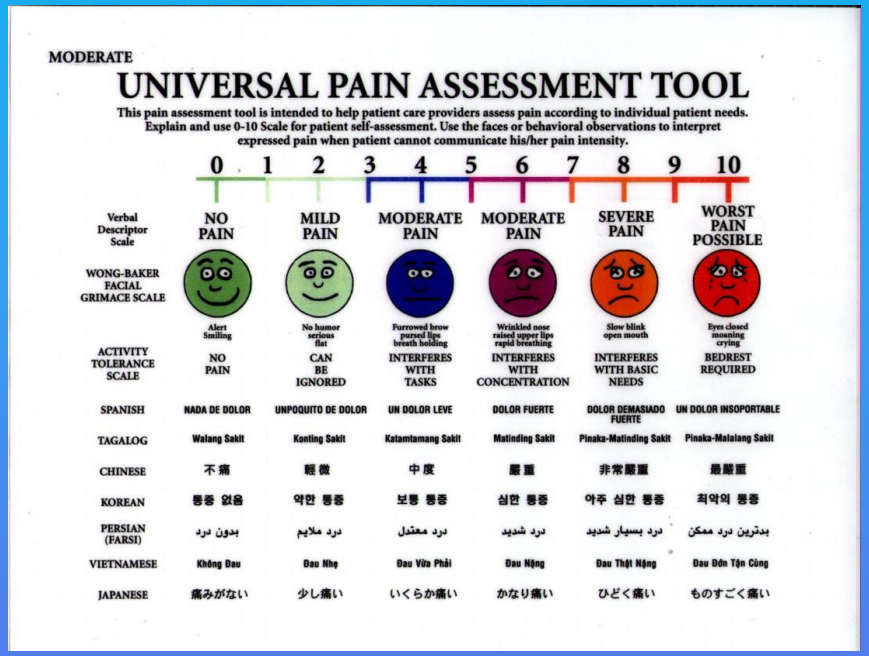
Objective assessment of pain

Assessment- Measurement Tools

Pain history

Examination

- Psychometric
  - Subjective pain scores
    - VAS, pain descriptors
  - Affective
    - Anxiety depression FUNCTIONALITY- disability
- Psychophysical
  - Neurophysical tests - neuropathic area
    - Cold warm / Mechanosensory / Vibration
    - Special sensory =Taste

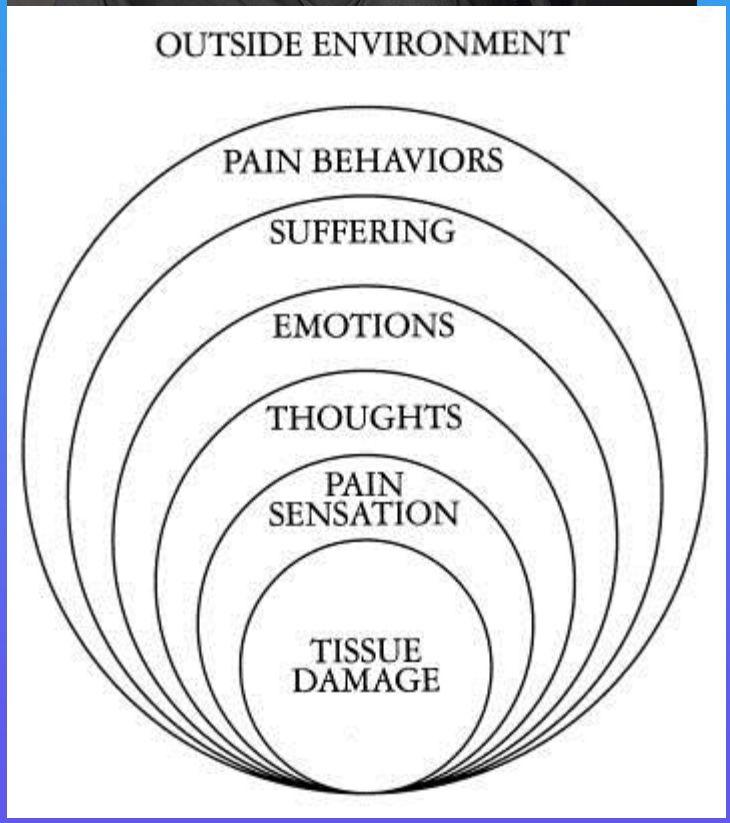


Pain history

- Site
- Duration
- Frequency
  - Constant (burning throbbing)
  - Spontaneous / evoked (cause / relief)
- Character
  - Type
    - burning, stabbing
  - Intensity
- Persistent / intermittent
- Localisation
- Radiation
- Associated signs -redness swelling

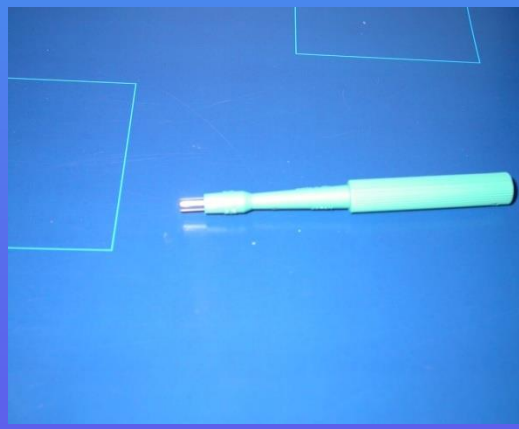
Psychometics

- Measure
  - Affective
    - Anxiety
    - Depression
    - Beliefs
    - Fear
    - Anger
    - Coping



Assessment - neuropathy

- VAS
  - At rest
  - Dynamic allodynia
  - Cold allodynia
  - capsaicin
- Mechanosensory
  - Von Frey
  - Neuropathic area
- Local analgesia
- Thermo sensory
- Biopsy



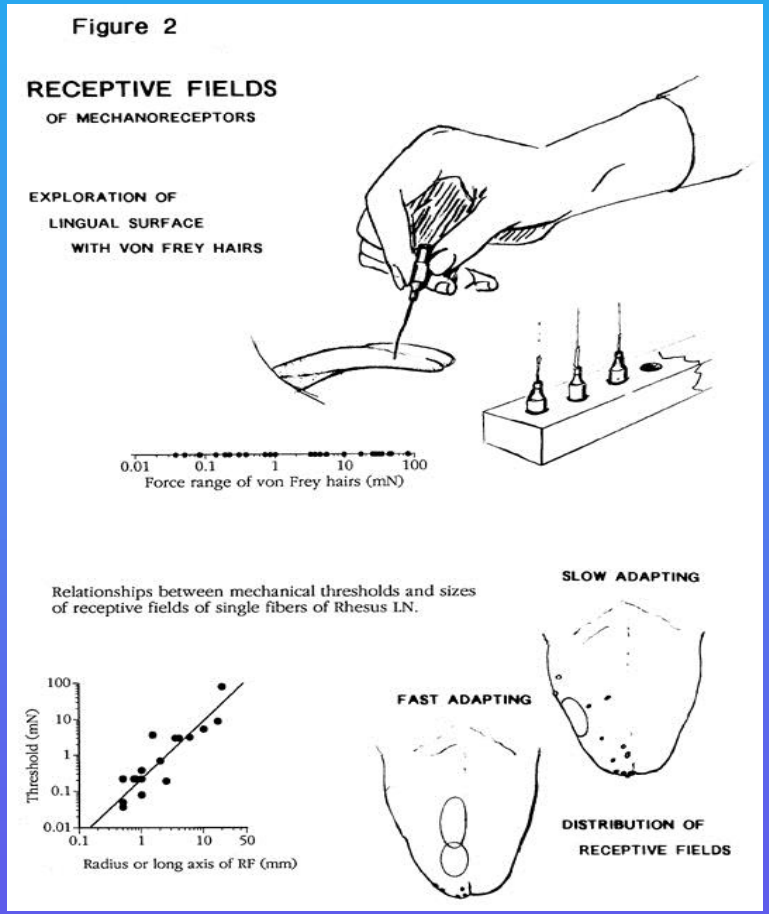
What are the problems?

With current assessment of trigeminal function

Solely mechanosensory (large fibres only)

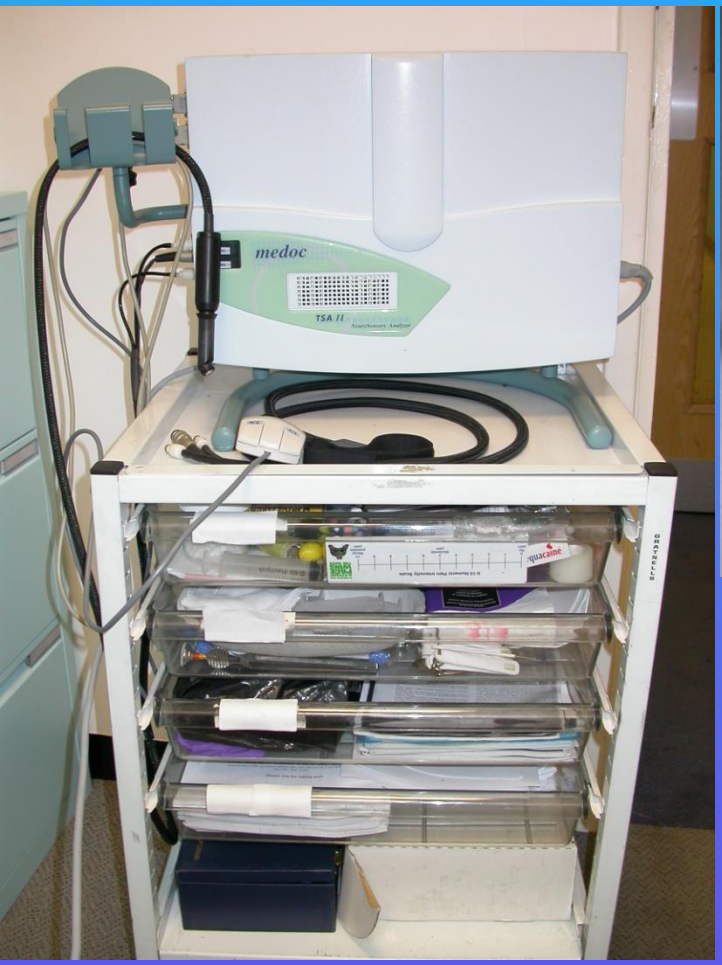
Taste tests unreliable

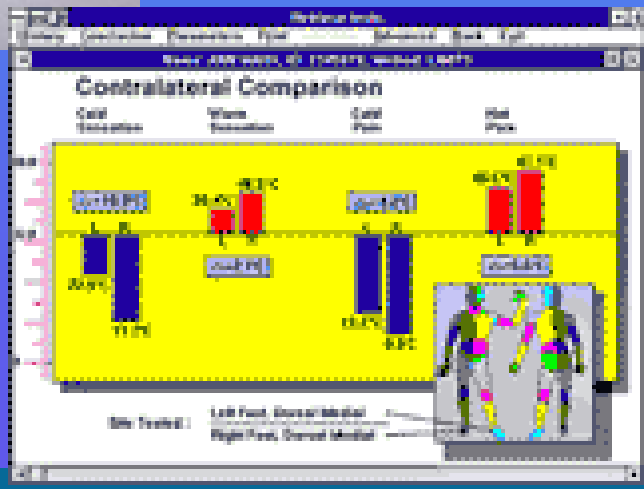
Pain and altered sensation often over looked



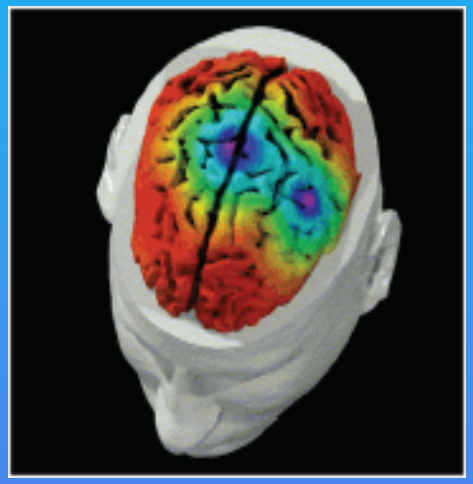
Psycho physical testing

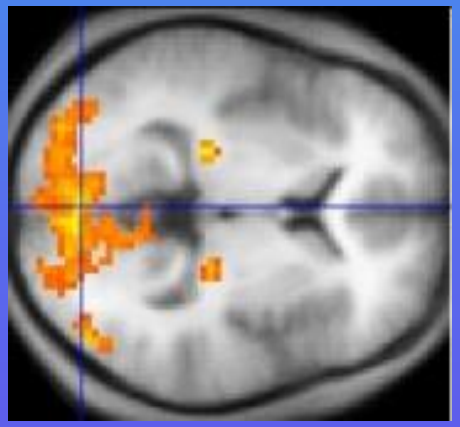
Quantitative thermo sensory testing

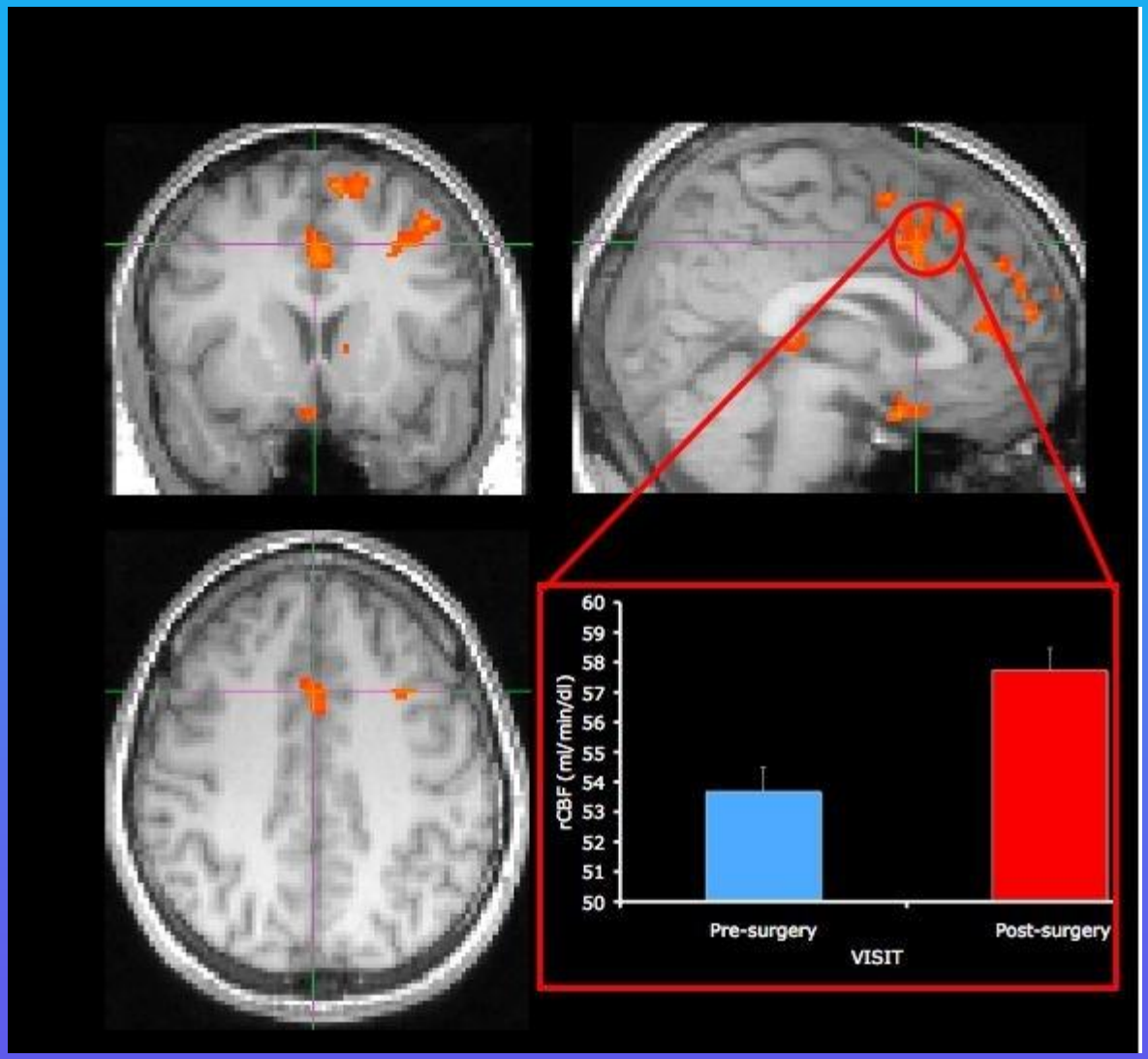




Assessment fMRI functional magnetic resonance imaging





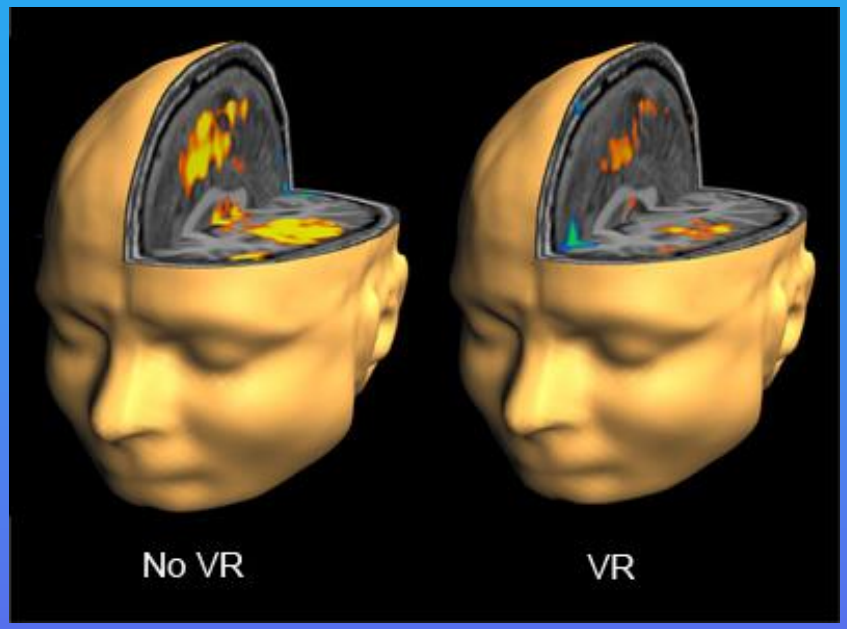


Management will depend on

Inflammatory or neuropathic pain?

Patient factors

Environment



The future.....

Prevention of chronic pain

Earlier recognition

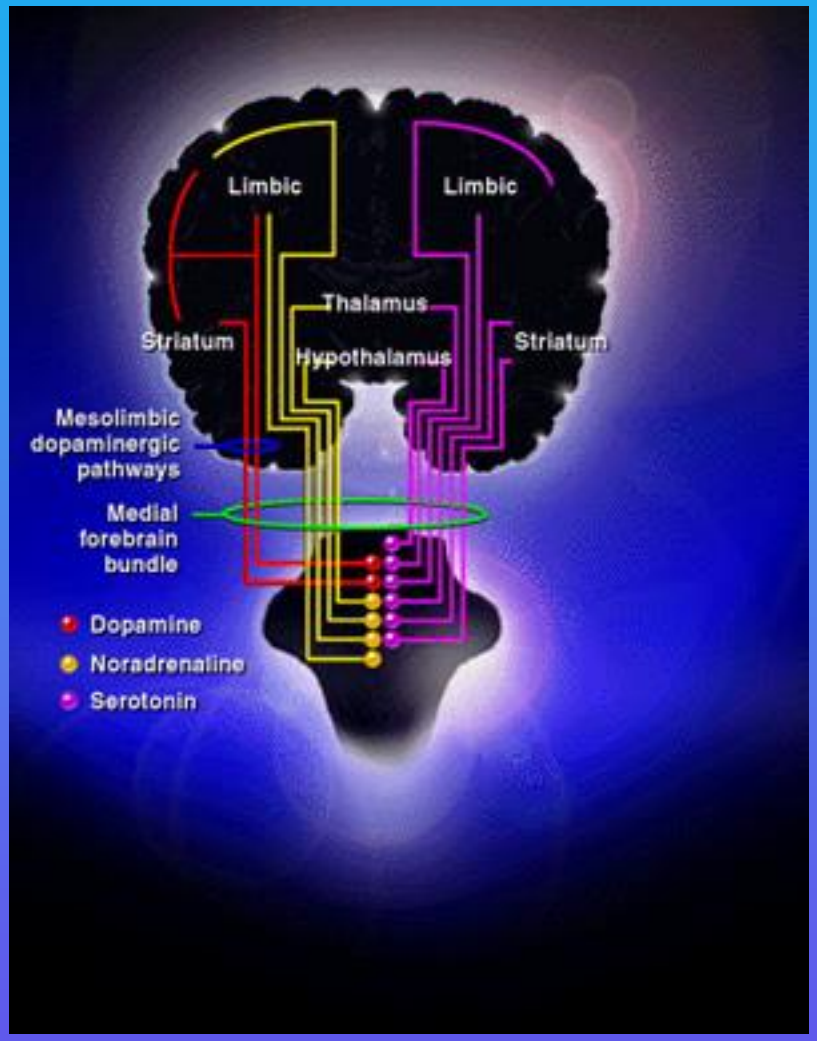
Tailored individual treatment

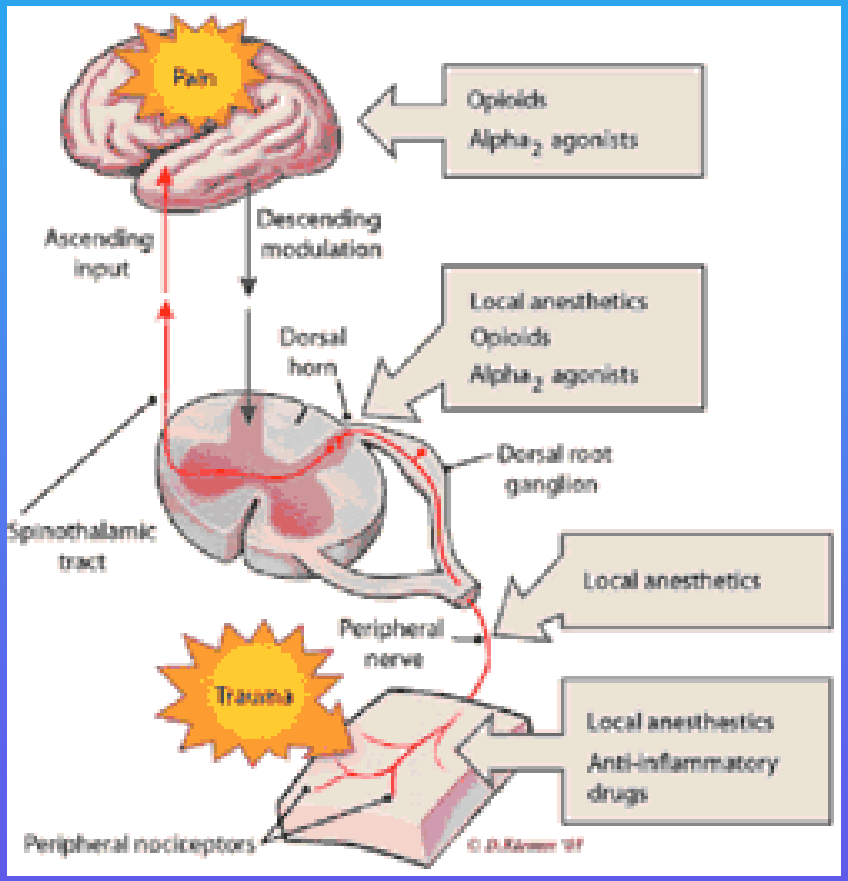
Thank you

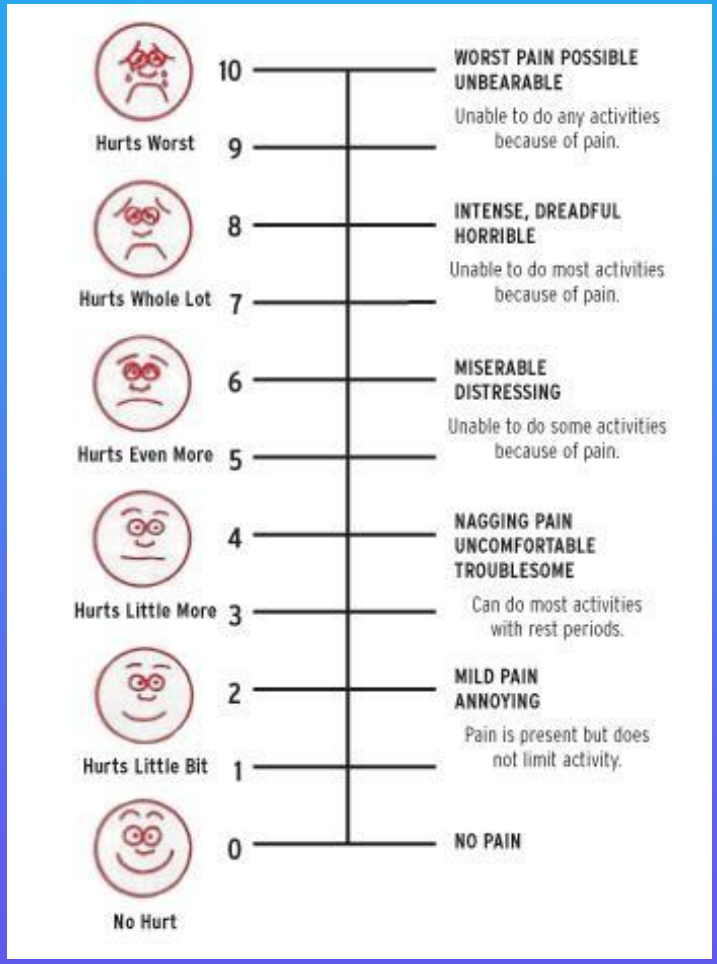
Neural propagation of pain

Where do drugs work?

- NSAIDS peripheral block - cyclo oxygenease
- Paracetamol ?central block – cyclooxygenase
- Opiates central block of NMDA receptors
- Local analgesia blocks all sodium nerve channels (motor and sensory)
- Sedation blocks central GABA receptor pathway = anxiolytic




Pain
Opioids
Alpha2 agonists
Ascending input
Descending modulation
Local anesthetics
Opioids
Alpha2 agonists
Dorsal horn
Dorsal root ganglion
Spinothalamic tract
Local anesthetics
Peripheral nerve
Trauma
Local anesthetics
Anti-inflammatory drugs
Peripheral nociceptors


10
WORST PAIN POSSIBLE
UNBEARABLE
Unable to do any activities because of pain.
Hurts Worst
9
8
INTENSE, DREADFUL
HORRIBLE
Unable to do most activities because of pain.
Hurts Whole Lot
7
6
MISERABLE
DISTRESSING
Unable to do some activities because of pain.
Hurts Even More
5
4
NAGGING PAIN
UNCOMFORTABLE
TROUBLESOME
Can do most activities with rest periods.
Hurts Little More
3
2
MILD PAIN
ANNOYING
Pain is present but does not limit activity.
Hurts Little Bit
1
0
NO PAIN
No Hurt

Visual Analogue Scales

anchors : no pain max pain

eideneurolearningblog.blogspot.com/2005_02_25...

:

www.mindhacks.com/blog/linkage/index.html

---

10 cm line

Circle the words below that best described your pain
Use only one word in each group.
Lease out any group if the words are unsuitable.

1	2	3	4
1 Flickering	1 Jumping	1 Pricking	1 Sharp
2 Quivering	2 Flashing	2 Boring	2 Cutting
3 Pulsing	3 Shooting	3 Drilling	3 Lacerating
4 Throbbing		4 Stabbing	
5 Beating		5 Lancinating	
6 Pounding			

5	6	7	8
1 Pinching	1 Tugging	1 Hot	1 Tingling
2 Pressing	2 Pulling	2 Burning	2 Itchy
3 Gnawing	3 Wrenching	3 Scalding	3 Smarting
4 Cramping		4 Searing	4 Stinging
5 Crushing			

9	10	11	12
1 Dull	1 Tender	1 Tiring	1 Sickening
2 Sore	2 Taut	2 Exhausting	2 Suffocating
3 Hurting	3 Rasping		
4 Aching	4 Splitting		
5 Heavy			

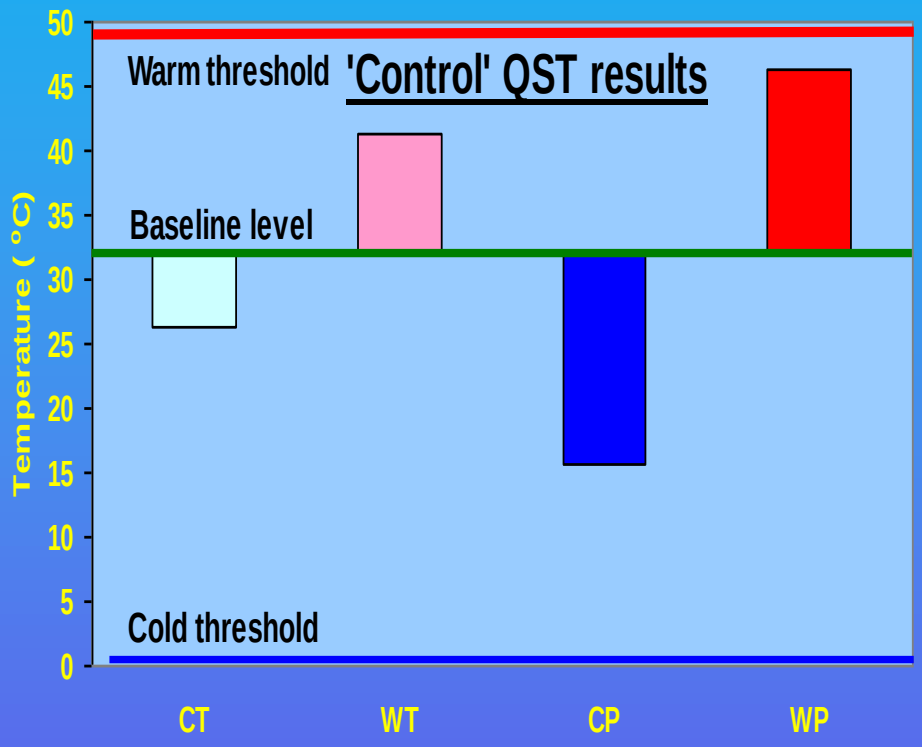
13	14	15	16
1 Fearful	1 Punishing	1 Wretched	1 Annoying
2 Frightful	2 Gruelling	2 Blinding	2 Troublesome
3 Terrifying	3 Cruel		3 Miserable
	4 Vicious		4 Intense
	5 Killing		5 Unbearable

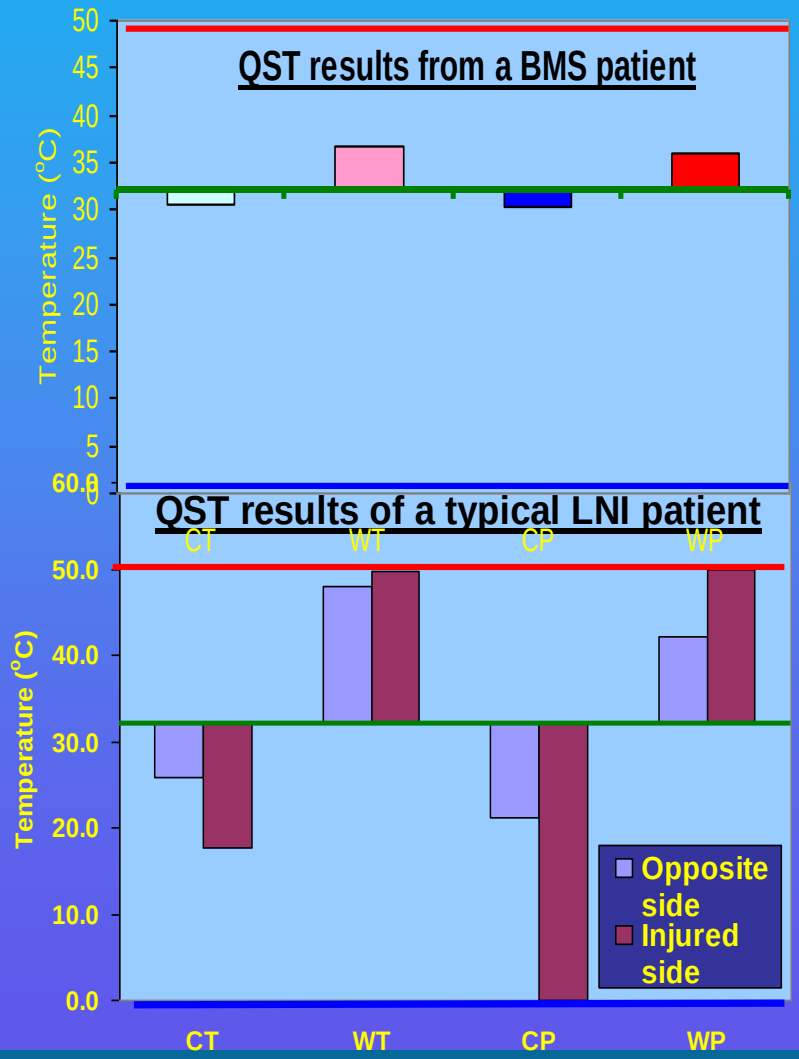
17	18	19	20
1 Spreading	1 Tight	1 Cool	1 Nagging
2 Radiating	2 Numb	2 Cold	2 Nauseating
3 Penetrating	3 Drawing	3 Freezing	3 Agonizing
4 Piercing	4 Squeezing		4 Dreadful
	5 Tearing		5 Torturing

McGill Pain Questionnaire

Descriptive WORDS

Sample thermal sensory results





Codes:

CT = Cool Threshold CP = Cold pain

WT = Warm Threshold WP = Warm pain

Impact of orofacial pain

70% psychological impact

Locker & Grushka 1987

48% psychosocial impact

Richards & Slade 1996

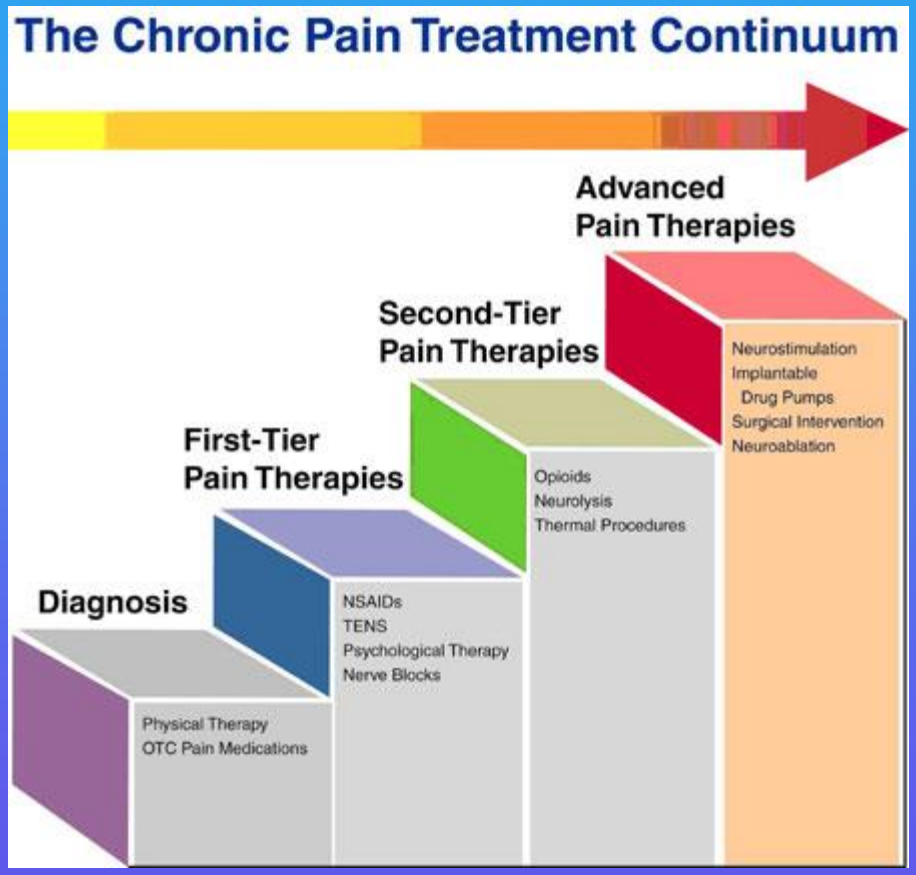
In TMJ pain

29% high disability resulting in unemployment

Von Korff et al 1992

64% decreased efficiency at work

Dao et al 1994


The Chronic Pain Treatment Continuum
Advanced
Pain Therapies
Neurostimulation
Implantable
Drug Pumps
Surgical Intervention
Neuroablation
Second-Tier
Pain Therapies
Opioids
Neurolysis
Thermal Procedures
First-Tier
Pain Therapies
NSAIDs
TENS
Psychological Therapy
Nerve Blocks
Diagnosis
Physical Therapy
OTC Pain Medications