The genetic and biomolecular basis for trigeminal pain

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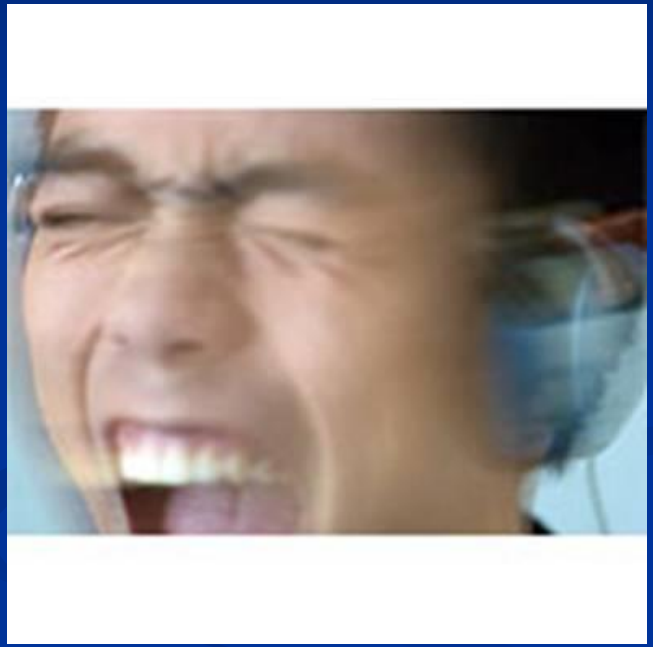
An update

- What is pain?
- Trigeminal pain
- How do we feel it?
- What influences perception of pain?
- Bio-molecular basis of pain
- Genetic basis of pain



What is pain?

- Subjective sensation
  - with physical and psychological effects
- Individual response
  - dependant on
  - age / gender / experience / personality / anxiety
  - settings / trust in clinician / fatigue
- Organic and or psychological cause
- 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"

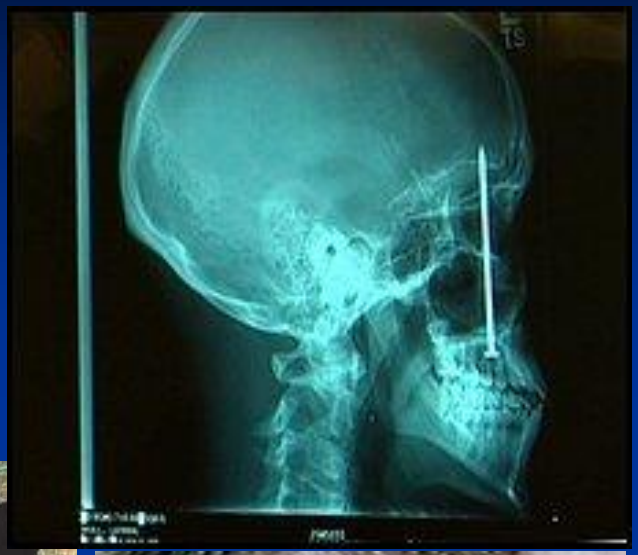
(IASP, 1979)

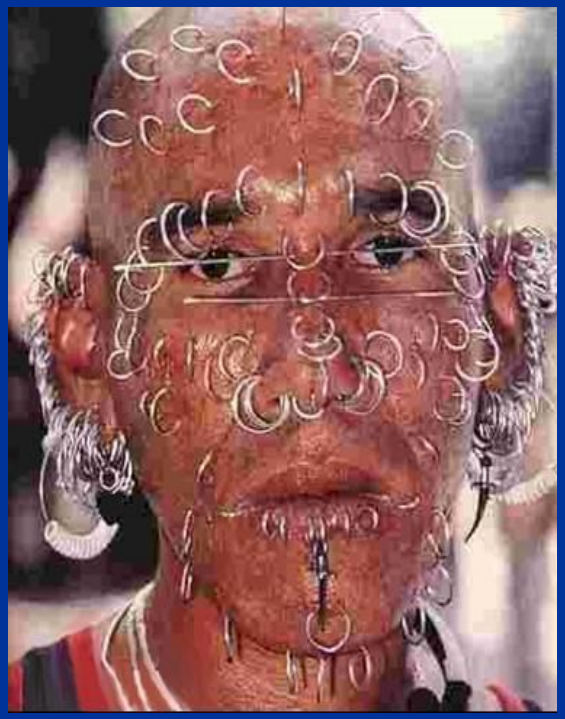
Consequences of pain

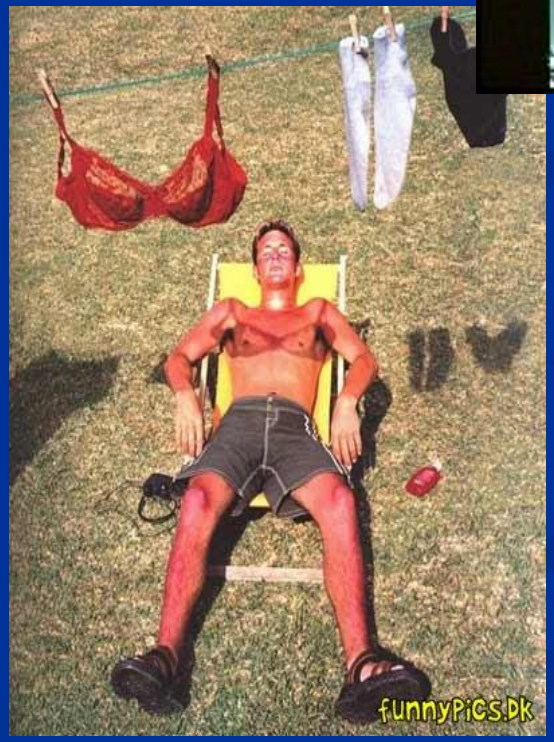
- Side effects are a major hurdle in treating chronic pain, which costs the United States around $100 billion annually in treatment and lost wages.
- About 50 million adults in the United States suffer from chronic or persistent pain, according to an article on the subject in the journal Science.
- It accounts for more than 20 percent of doctor's visits and 10 percent of the trillions of dollars spent on health care.

Pain - Acute

- 'Healthy pain' due to inflammation
- Infection / autoimmune / trauma
- thermal / mechanical / chemical
-

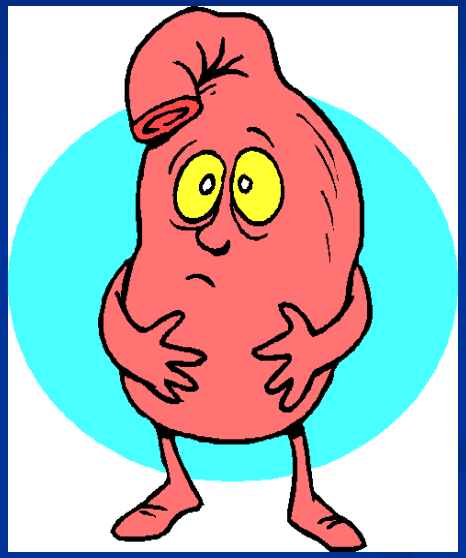




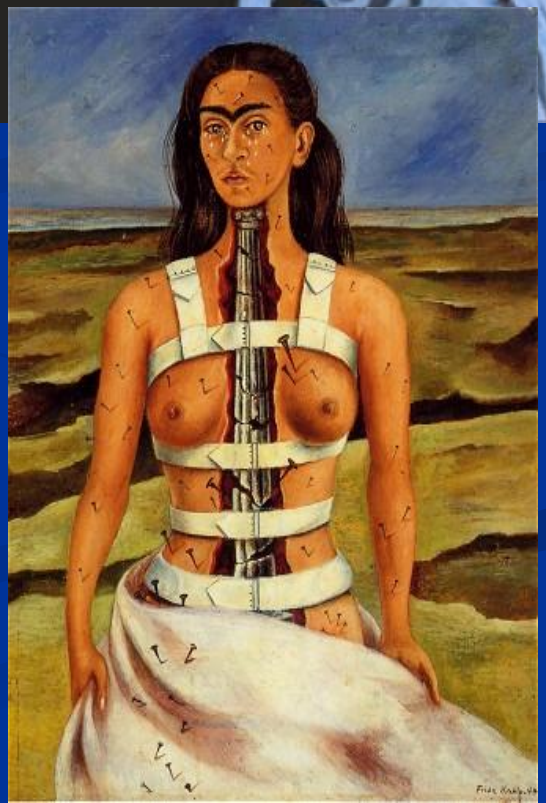


Chronic Pain

- **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

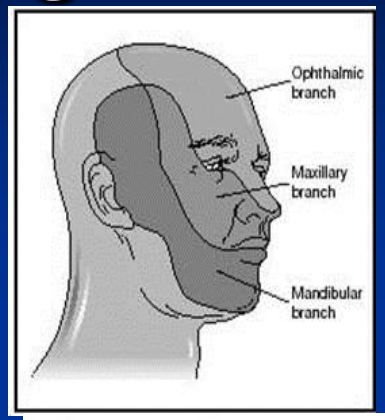
- 33% of US population suffer
- 13% work force is compromised
- USA $61.4 billion dollars/year lost on
- Diabetic and HIV neuropathy
- Accounts for £40 million GNP / year UK

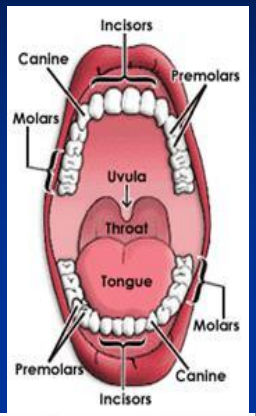
Why does pain become chronic?

- 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

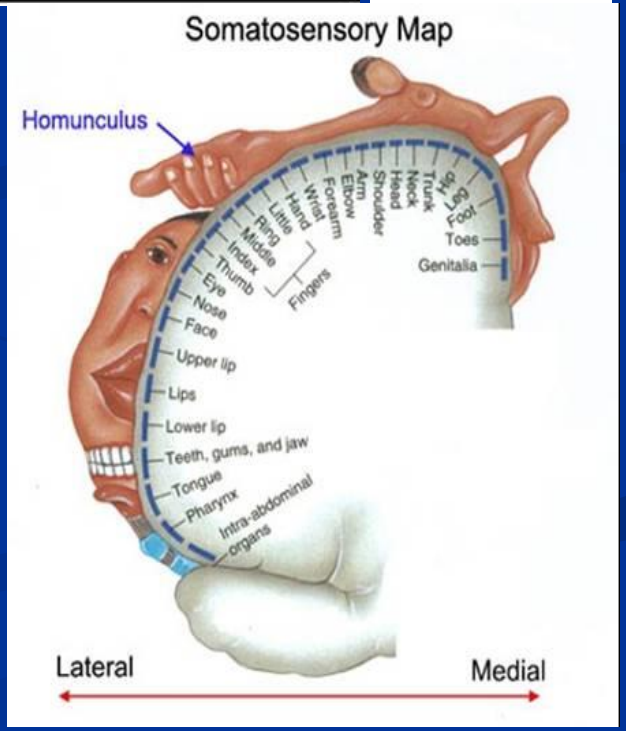
Trigeminal nerve

- 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

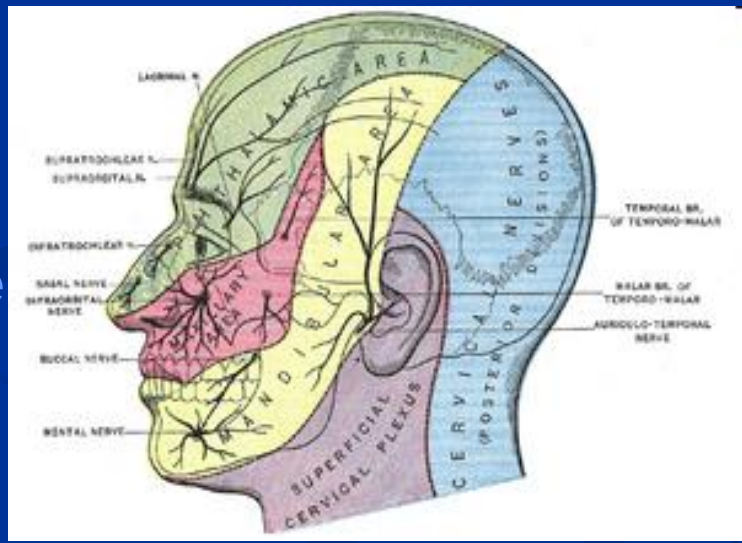
Trigeminal nerve- Function

- Largest of all cranial and sensory nerves
- General sensory and motor functions.
  - **Ophthalmic** (V1), **Maxillary** (V2) & **Mandibular** (V3)
- Clear geometry of the 3 divisions of the face

(no overlap)- for measures of somatotopic representation to stimuli

- Branches converge on the trigeminal ganglion

(TG) at Meckel's cave in middle cranial fossa.



Classification of Chronic orofacial pain

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

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

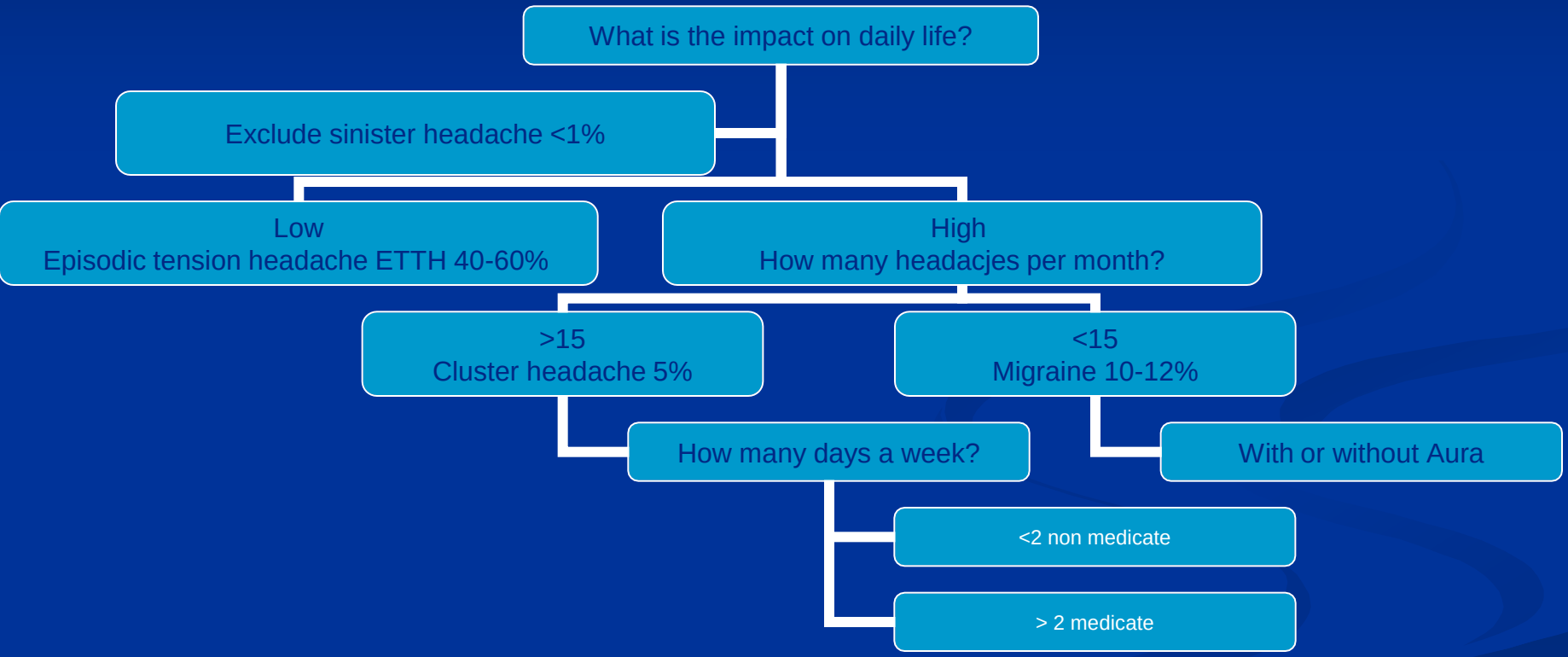
  8x a day to every other day for a period of 2 -12 weeks
- Tensions type headaches *30-78% population -Highest socioeconomic impact*

  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’

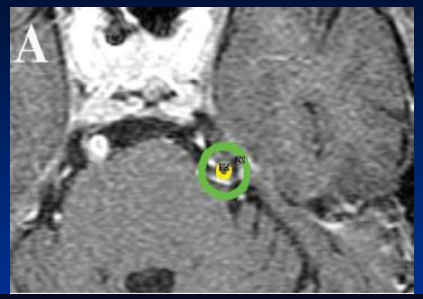
- Trigeminal neuralgia (TN)
  - Typical
  - Atypical
- Post herpetic neuralgia (PHN)
  - > 50 yrs 60% likely to develop pain post shingles
  - Ramsay Hunt syndrome
- Glossopharyngeal neuralgia
  - Acute pain pharynx, tongue base, mastoid regions
- Post traumatic V neuralgia
  - Lingual nerve injuries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

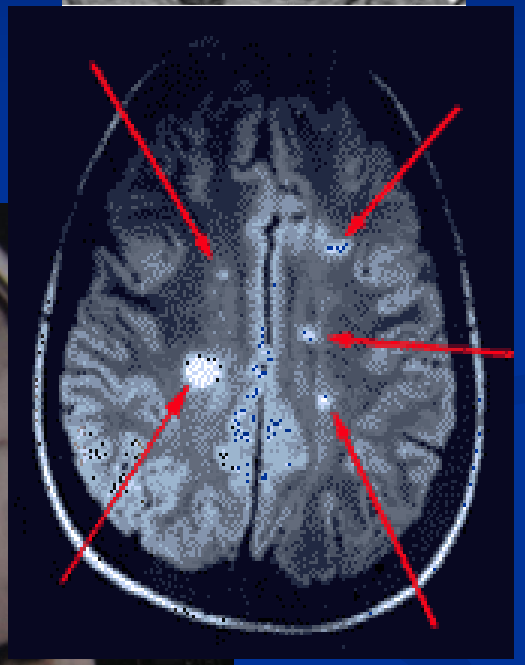
V neuralgia seen in patients with

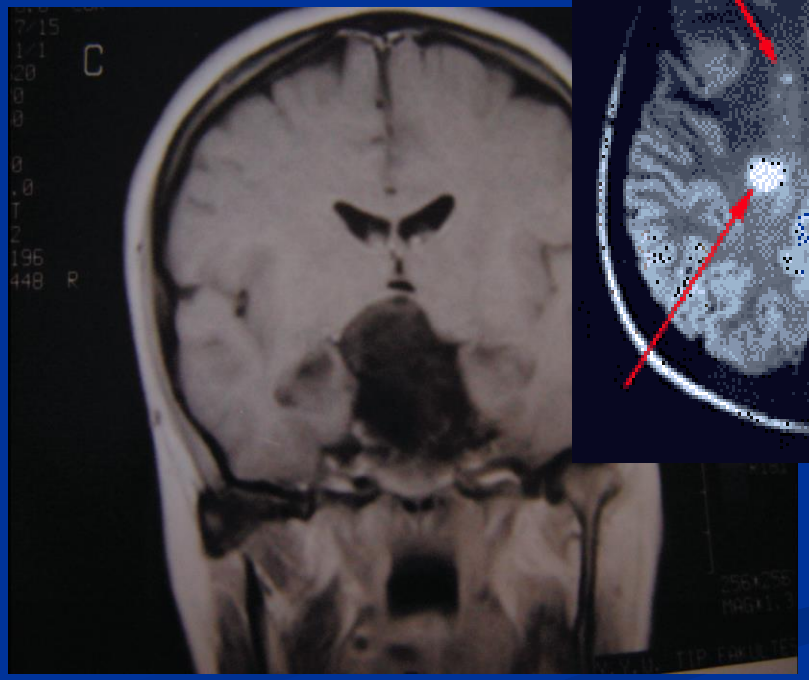
Diabetes
HIV
Chemotherapy
MS

Exlude central pathology

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

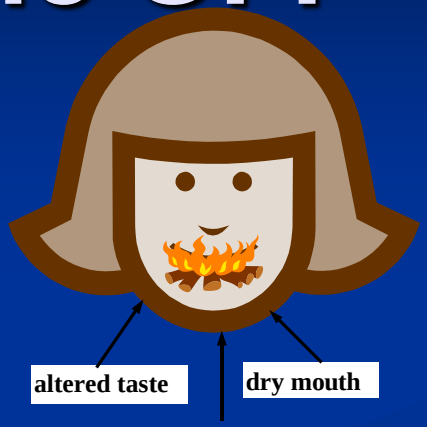


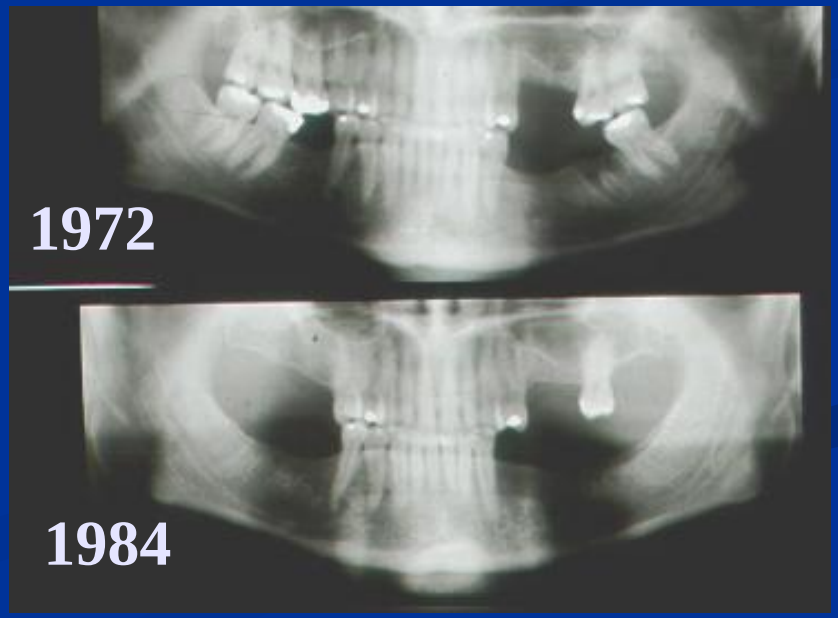




Idiopathic chronic OFP

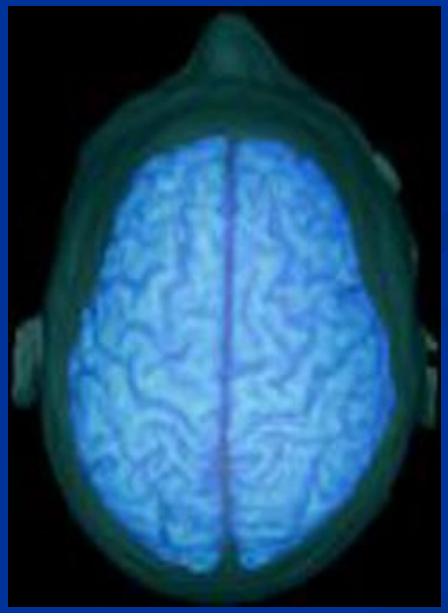
- TMJ pain
  - Functional - chewing gum
  - Arthritides
  - Derangement
- BMS
  - ? neuropathy
- Persistent idiopathic
  - Extraoral / facial
  - Intraoral / odontalgia





Patients in pain

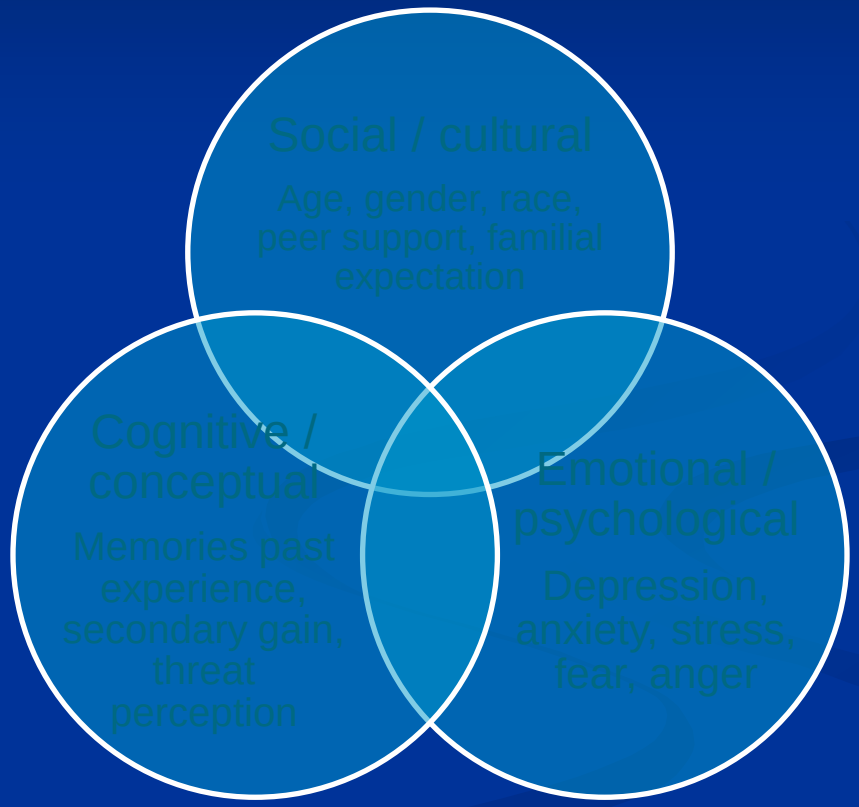
How do we feel the "ouch“?

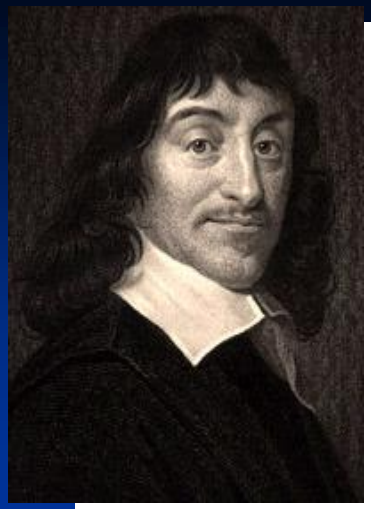


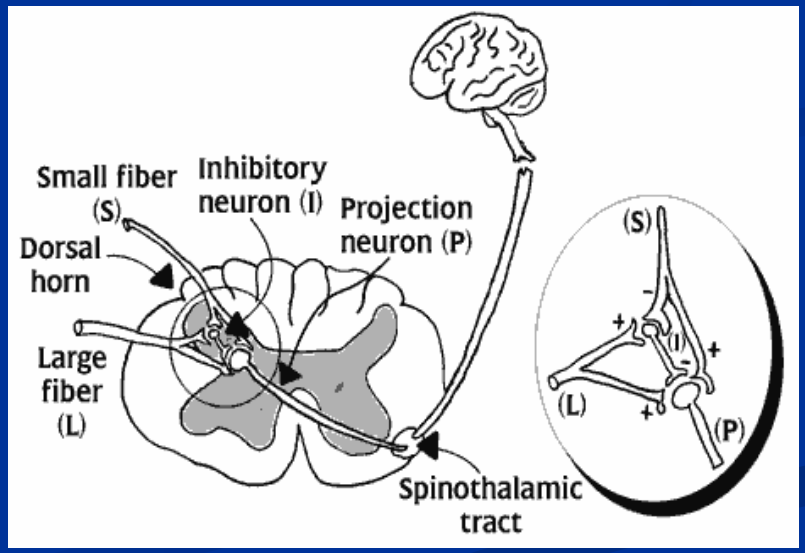
Pain Process

Bio psycho social Model

Nociception
Sensation
Behaviour
Suffering







Descartes 1650 in Stockholm

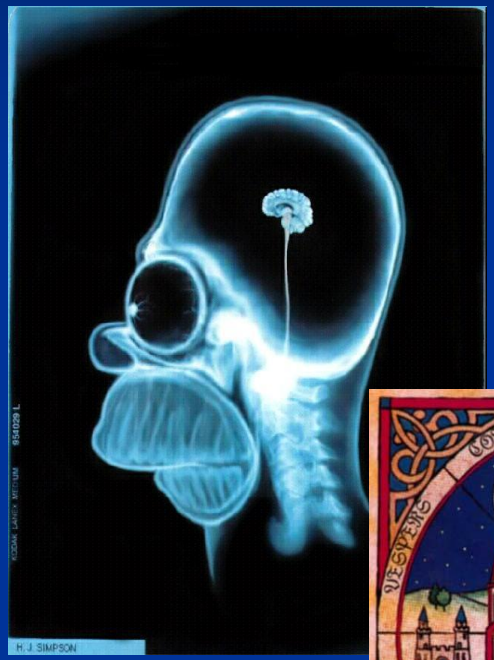
Canadian psychologist Ronald Melzak and British physiologist Patrick Wall 1965

Perception of pain

Perception of p

‘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.

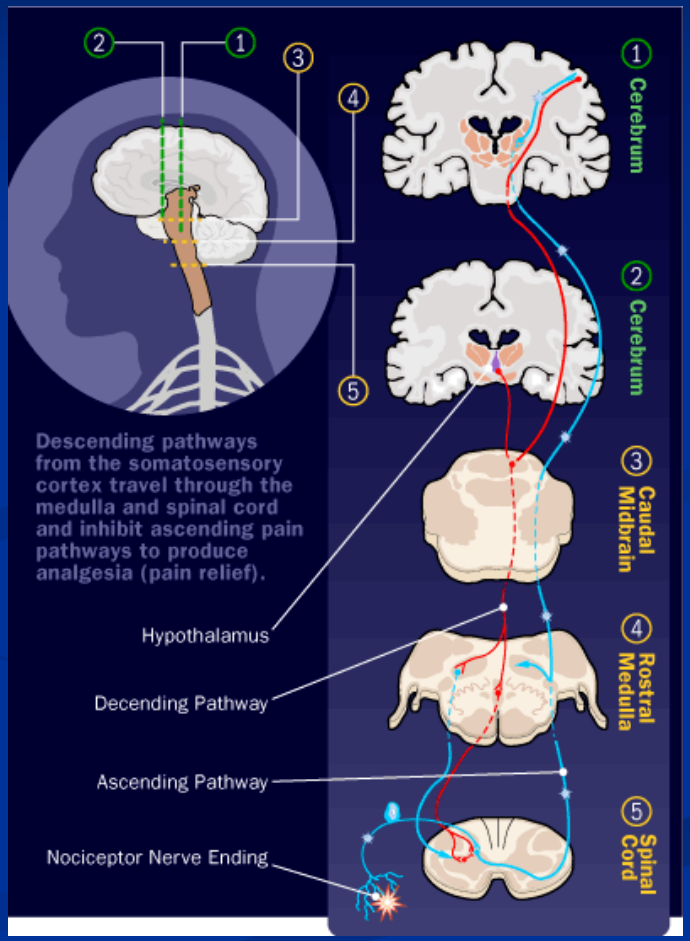
- Painful 'hot' temperatures activate the reward-associated structures, particularly in an area called the nucleus accumbens

- Dissociation and self harming

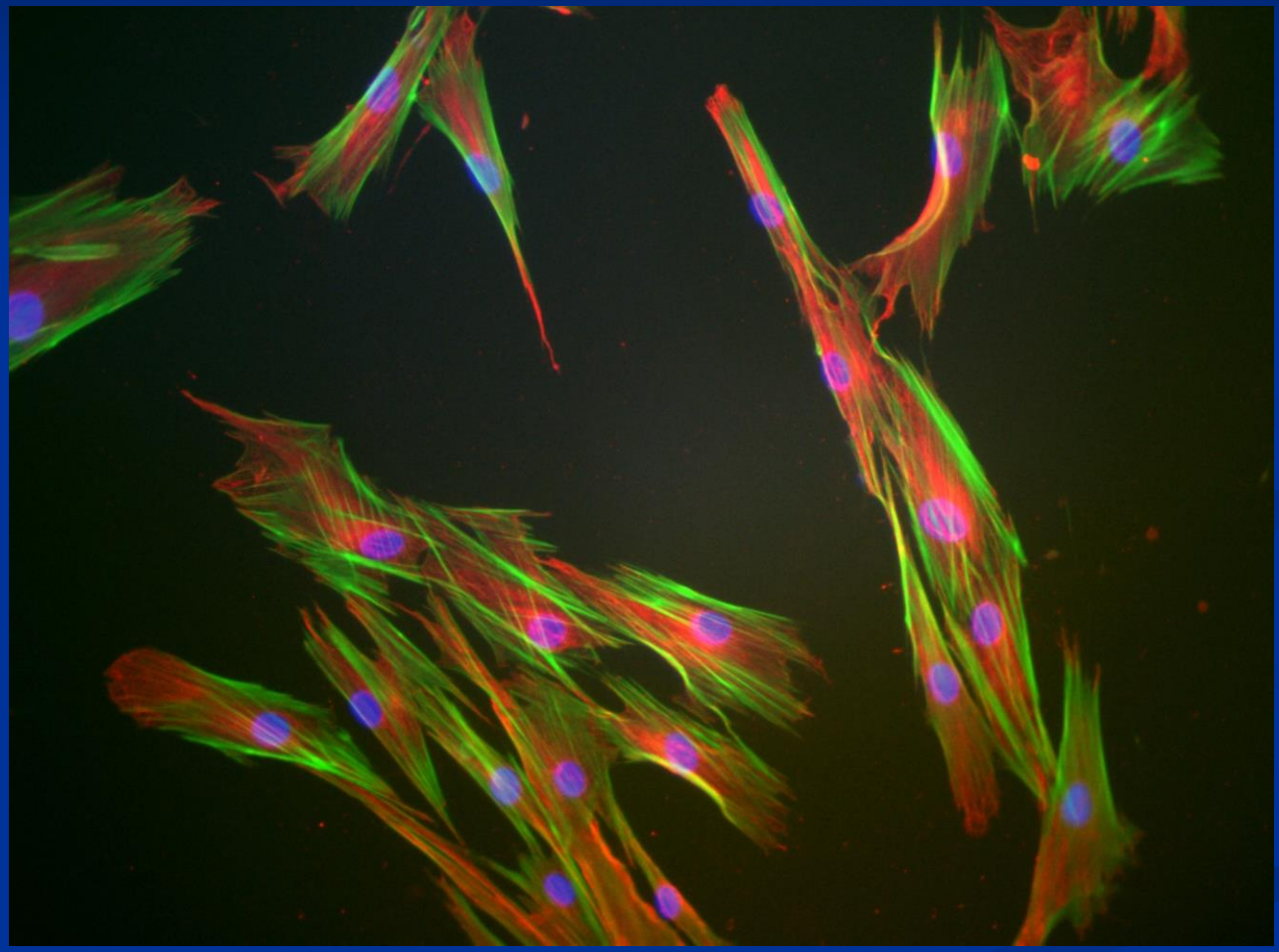
Noxious stimulus
What events unfold in the sensory system?

- 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

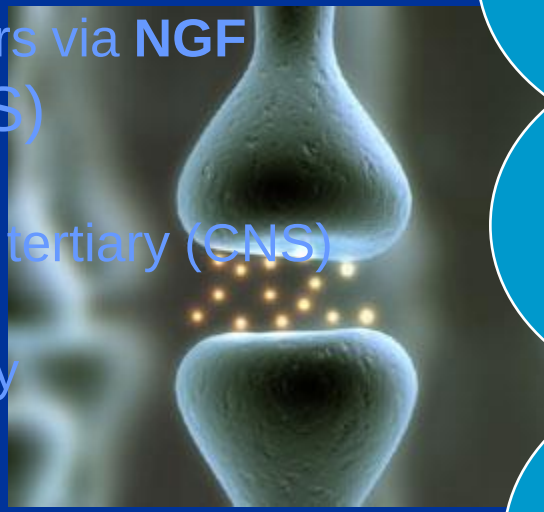
Reaction is Emotional and Physical



The bio-molecular basis of pain so far



- 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



Keratinocyte

Phospholipase A

Prostoglandins

Leukotrienes

Platelet
serotonin

H+ K+

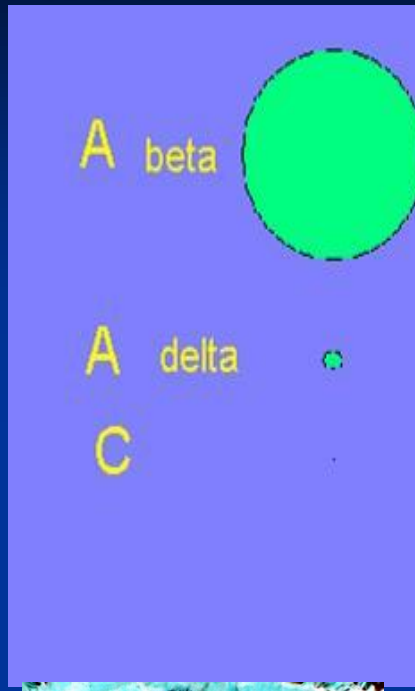
Mast cells

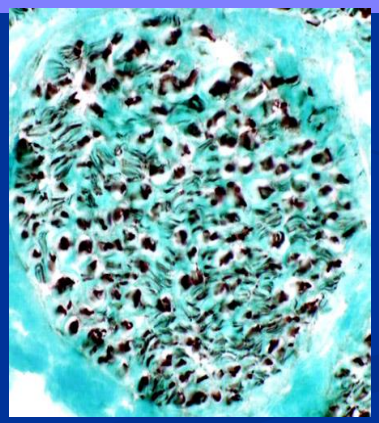
Bradykinin

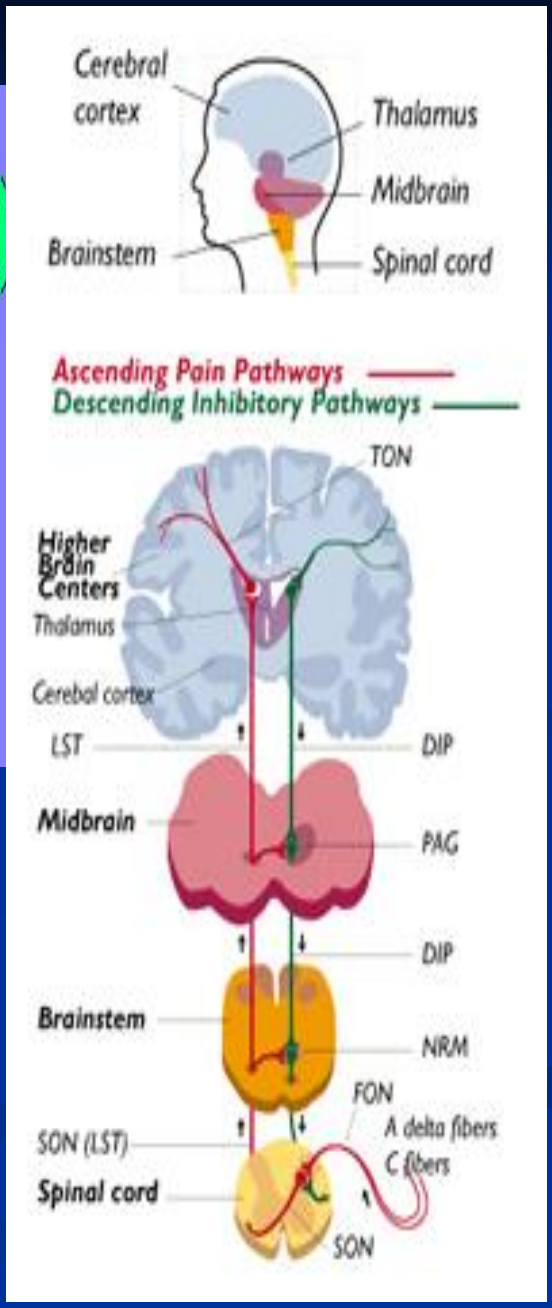
Nerve growth factor NGF

CNS/ PNS interaction

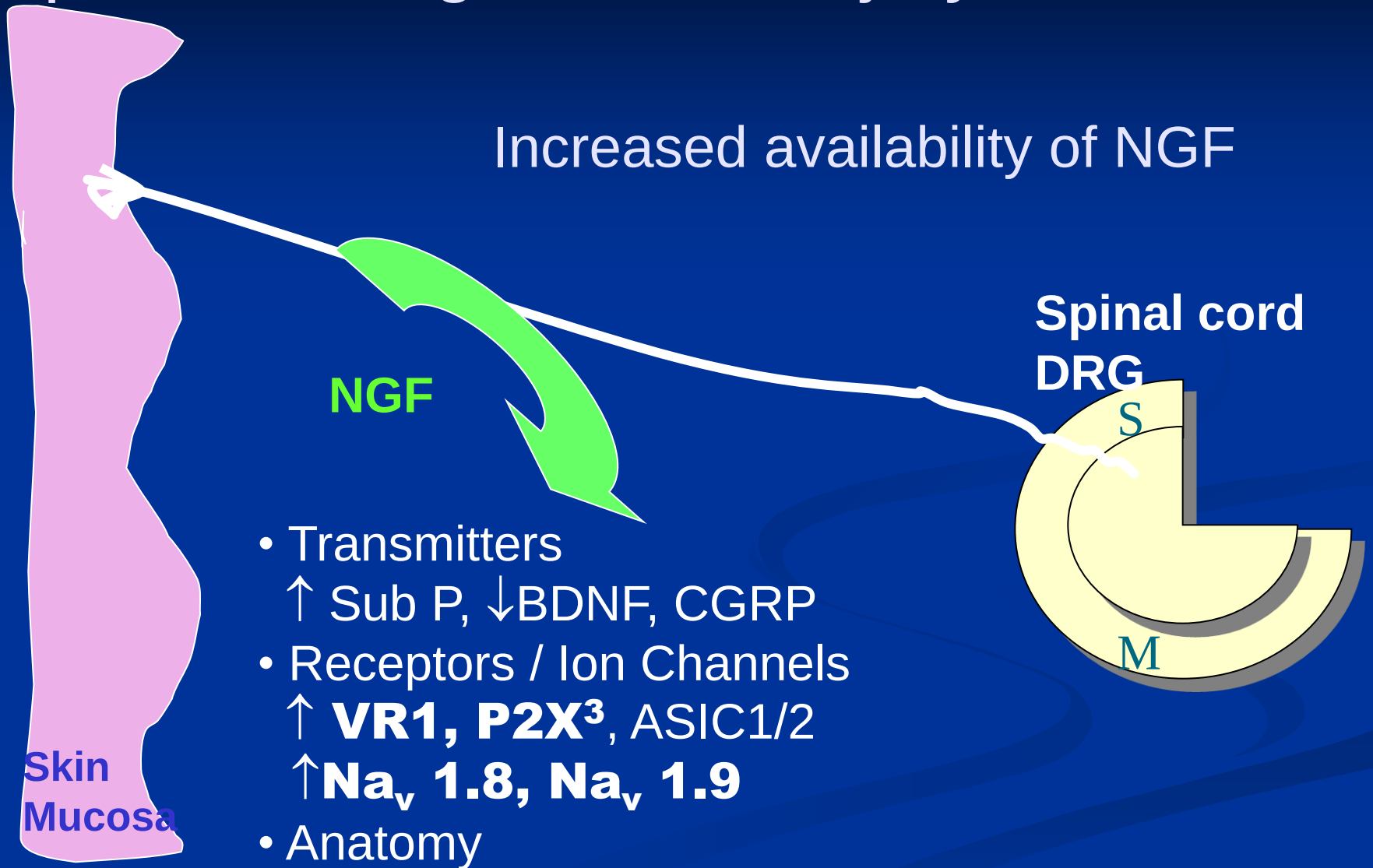
- Receptors
- Primary sensory nerve
  - A Delta and C fibres
- Secondary sensory nerve
  - Lamina I DRG
- Tertiary sensory nerve
  - Specific areas of the brain
    - Thalamus
    - Anterior cingulate cortex
    - S1 / S2
    - Insula
    - Brainstem







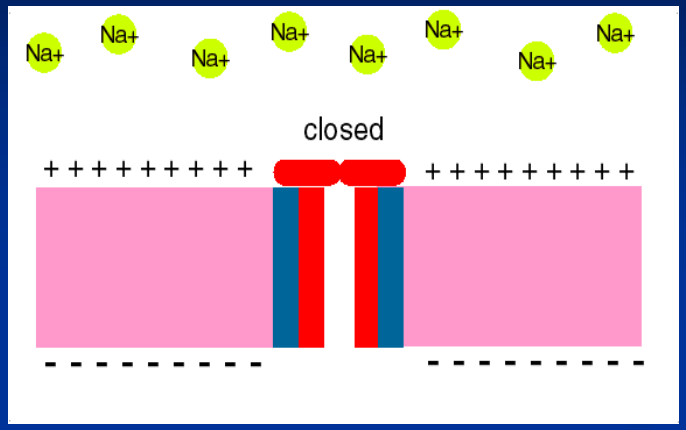
Peripheral changes due to injury

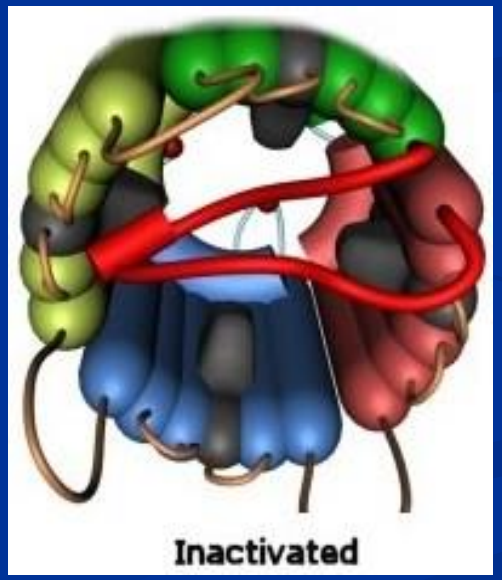


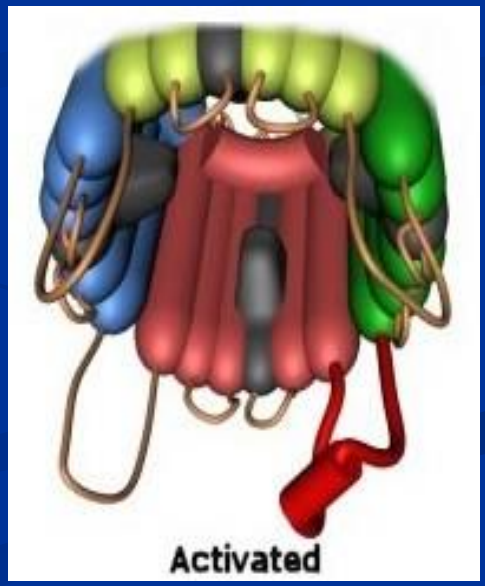
- Transmitters
  ↑ Sub P, ↓BDNF, CGRP
- Receptors / Ion Channels
  ↑ **VR1, $P2X^3$**, ASIC1/2
  ↑**Na_v 1.8, Na_v 1.9**
- Anatomy
  ↑GAP 43, innervation density

Specific pain receptors

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







Previous studies linking pain conditions and TRPV1 up regulation

TRPV1:	
Rectal hypersensitivity & faecal urgency	Chan et al., (2003)
Inflammation of the bowel	Yiangou et al., (2001)
Vulvodynia	Tympanidis et al., (2004)
Breast pain	Gopinath et al., (2005)
Overactive bladder	Brady et al., (2004); Avelino and Cruz, (2000)

Hypothesis

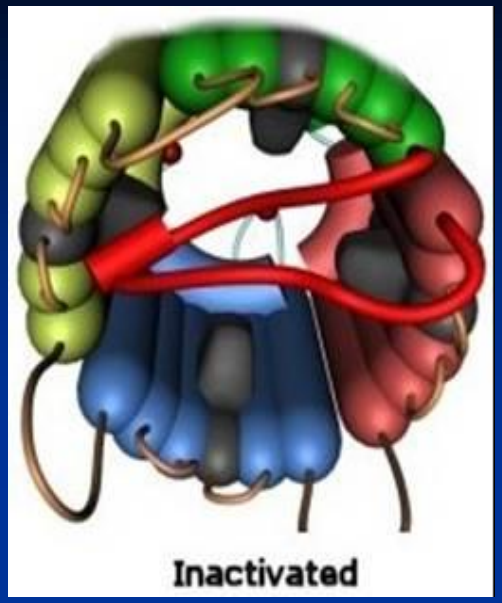
That nociceptors including:

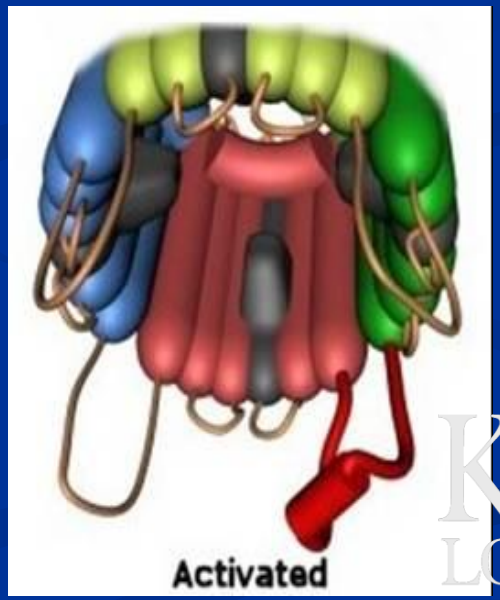
Sodium channel $Na_v1.8$ and 1.9

P2X3

TRPV1

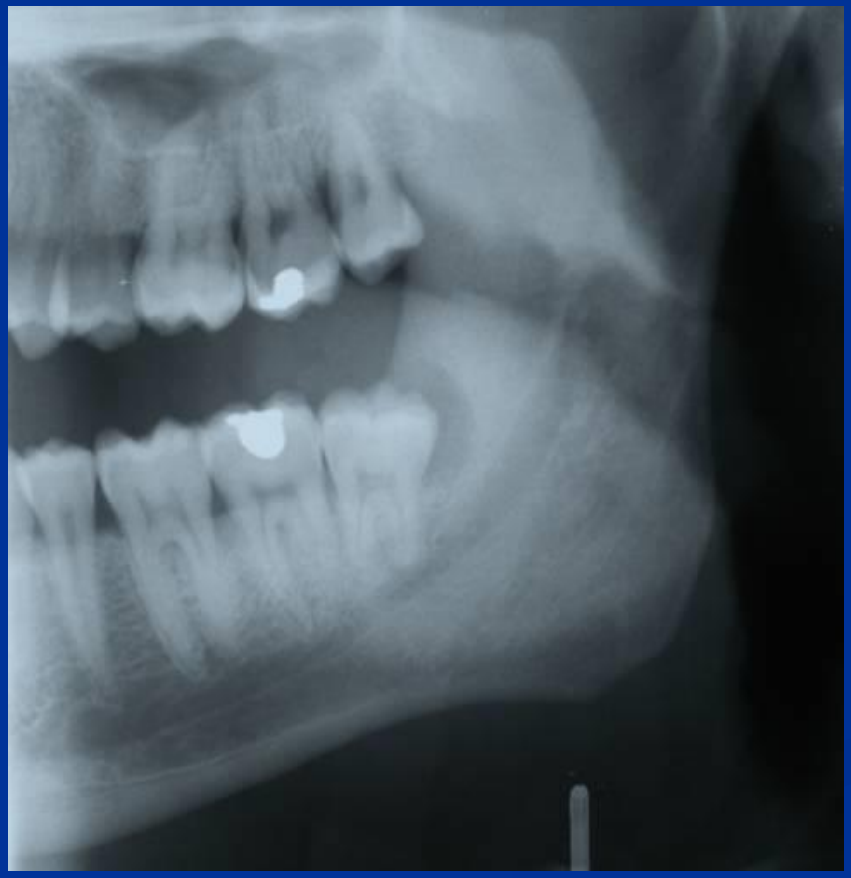
are up-regulated within dental pulpal nociceptors during dental pain?



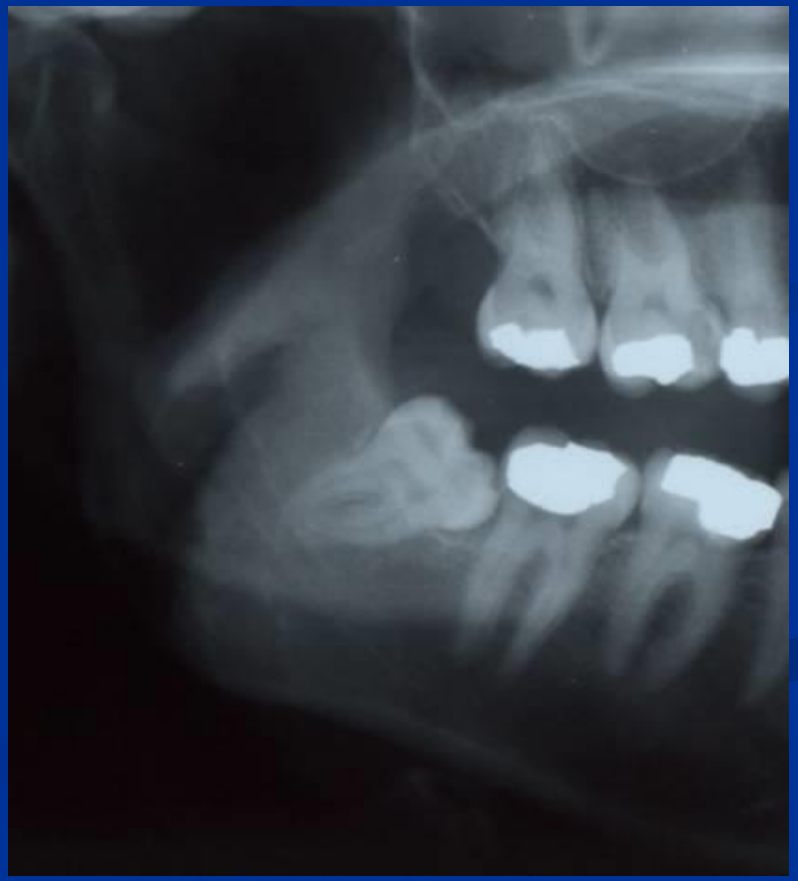


Method Subjects

Non painful (n=18)
Quiescent pericoronitis



Painful (n=10)
Pulpitis associated with caries



Receptors TRPV family (capsaicin/vanilloid receptor), **P2X3** (ATP activated channel)

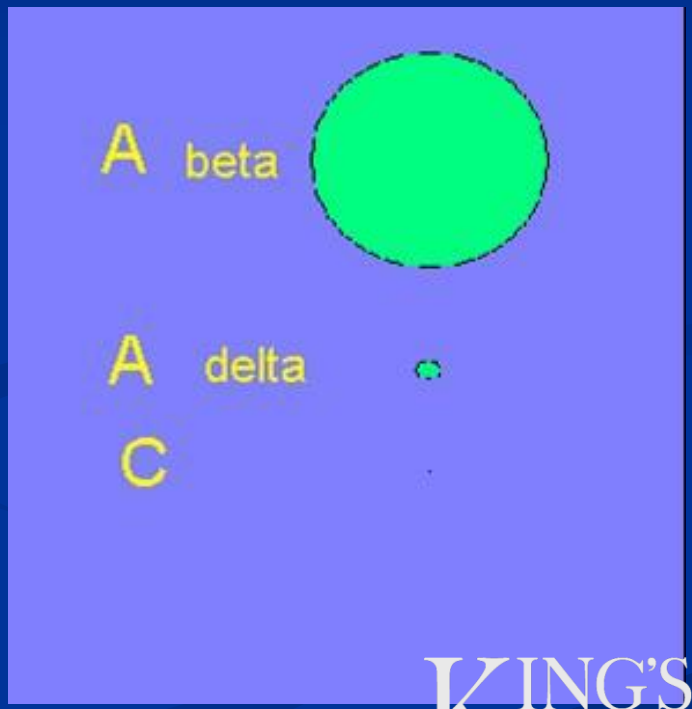
Nav 1.8 and **1.9** (sodium channels)

Preferentially expressed by nociceptors

Implicated in the pathophysiology of neuropathic pain

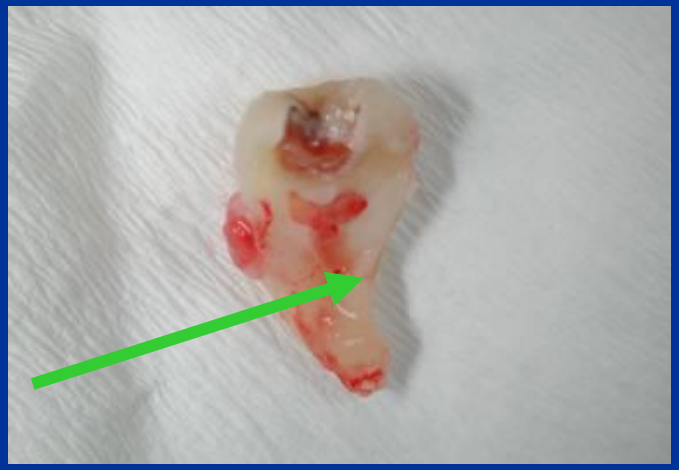
Antisense treatment of this channel reduces neuropathic pain in animal models

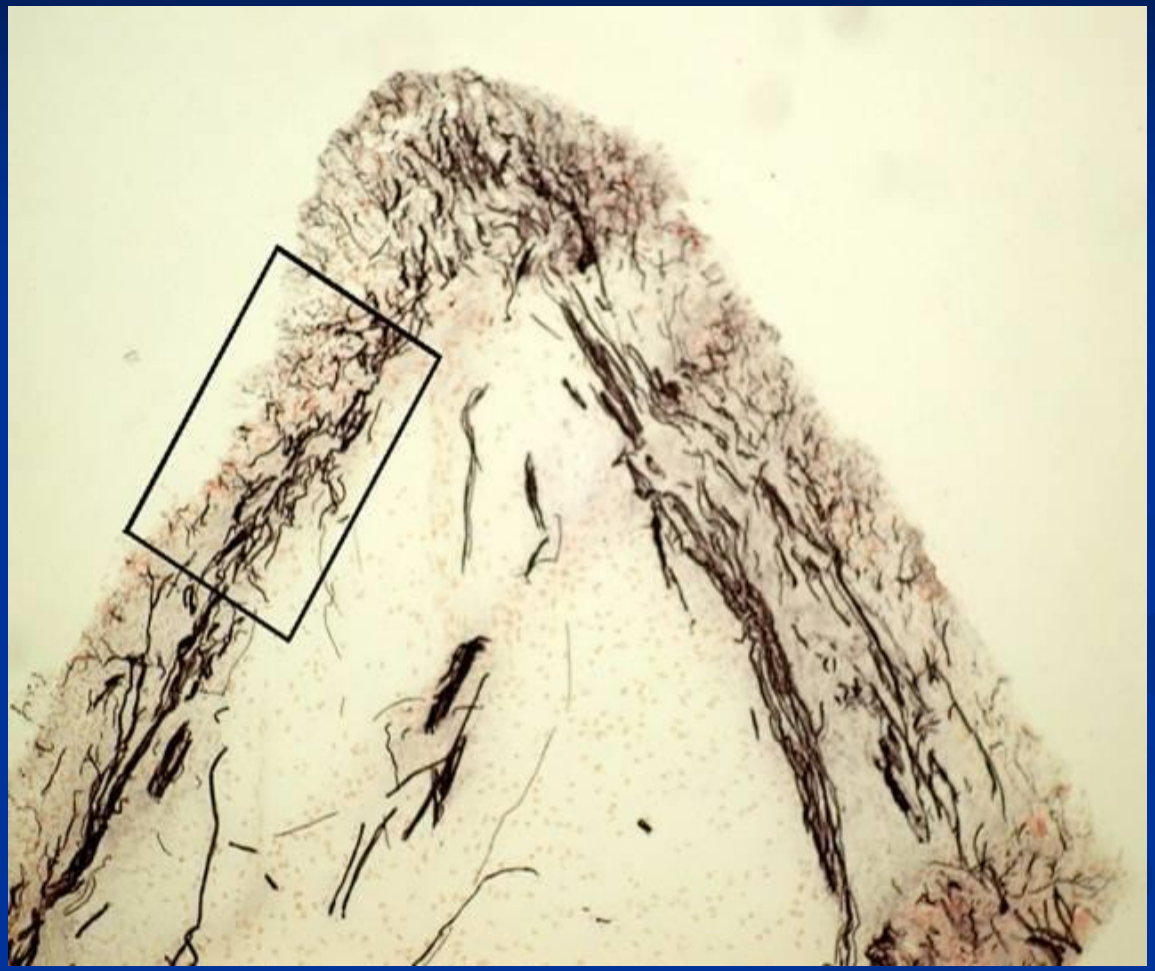
Null mutant mouse strains = absent pain behaviour



Methods Tissue sampling

- Extraction of pulp





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Method Immunohistochemistry

- embedded in OCT medium
- sections of 8μm
- monoclonal antibody neuronal marker neurofilament
- polyclonal antibody $Na_v1.8$ (K107)
- primary antibody attachment were revealed using avidin-biotin peroxidase method
- 1% aqueous neutral red to visualise nuclei
- Validation
  - positive staining human DRG neurons
  - no staining in pre-absorption

Method - Image analysis

- Computerized image analysis
  - Seescan Cambridge, UK
- Image capture
  - Olympus BX50 microscope (×40, objective)
  - Minimum of 5 fields at random
  - Ratio of the mean $Na_v1.8$ to neurofilament

- Statistics
  - Mann Whitney test compare ratios between groups
  - *P* values less than 0.05

  = significant

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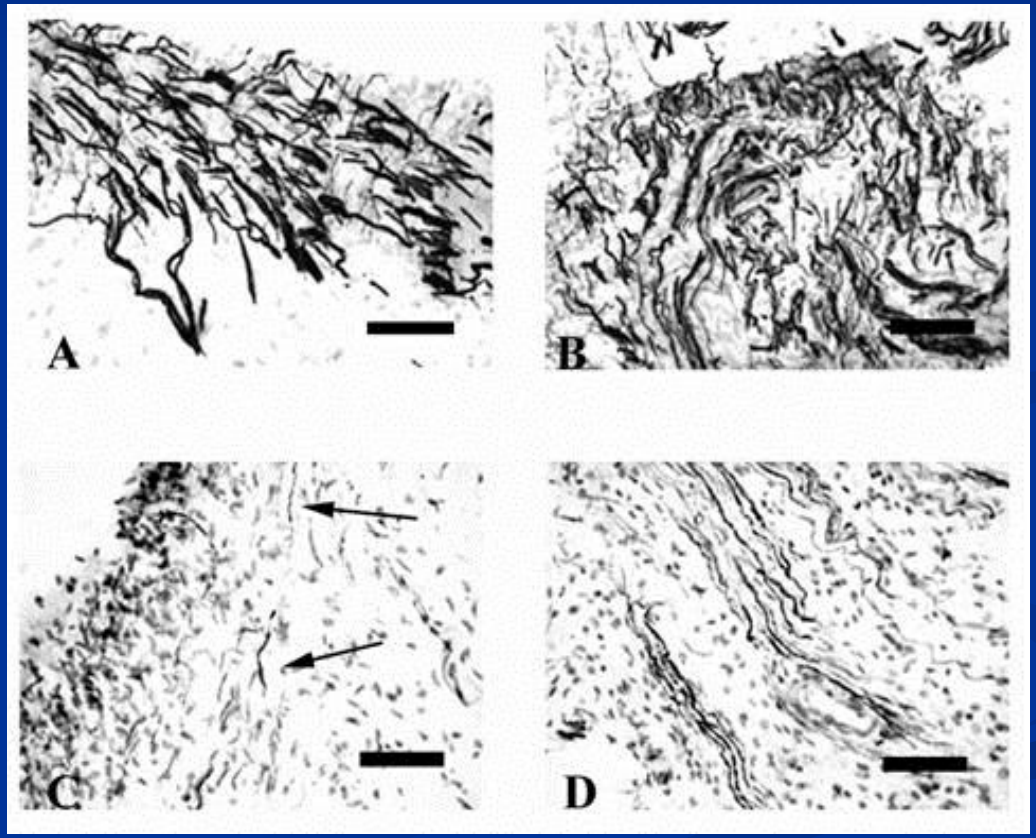
Results

Non-painful Painful

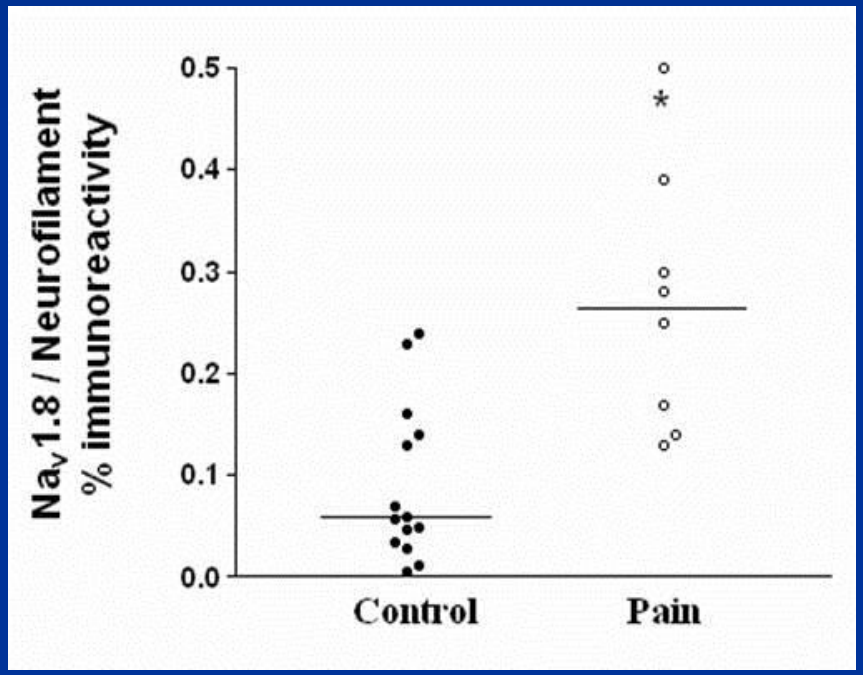
Neurofilament

$Na_v1.8$



Scale bar = 50 mm.

Results Nav 1.8



- $Na_v1.8$ to Neurofilament

  % area ratio
- non-painful 0.059

  (0.006- 0.24)
- painful 0.265

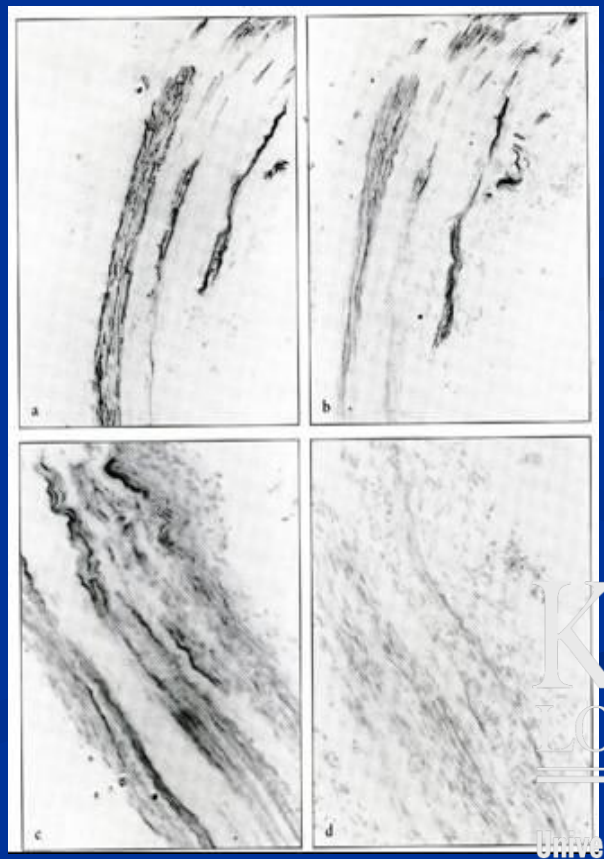
  (0.13-0.5)
- Significance

  $P = 0.0019$

TRPV receptors (and P2X3)

- Non painful pulp
- Painful pulp

NF TRPV1



Conclusions Pulpal pain

This study implicates $Na_v1.8$ with a pathophysiological role in human trigeminal pain

No increase in expression in TRPV1 or P2X3

The regulation and role of the sodium channel group deserves further investigation by;

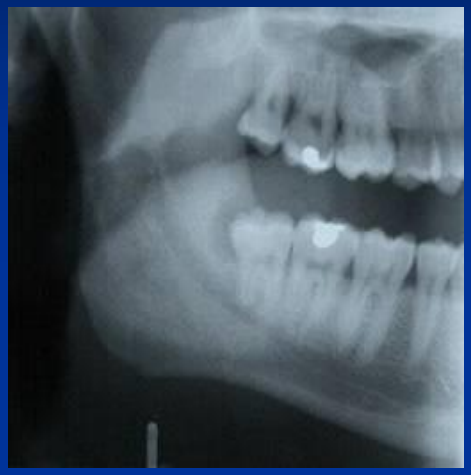
- Larger cross sectional studies
- Evaluation of the functionality of these receptors

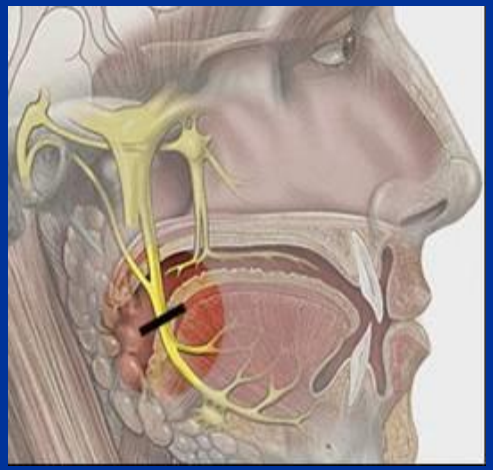
This model provides a novel method by which trigeminal nerve pain can be investigated and may provide the basis for future trials with novel channel blockers

Oral mucosal neuropathic pain

- Post traumatic nerve injury
  - Permanent anaesthesia/ paraesthesia/ pain of tongue or lower teeth and lip
- Burning mouth syndrome

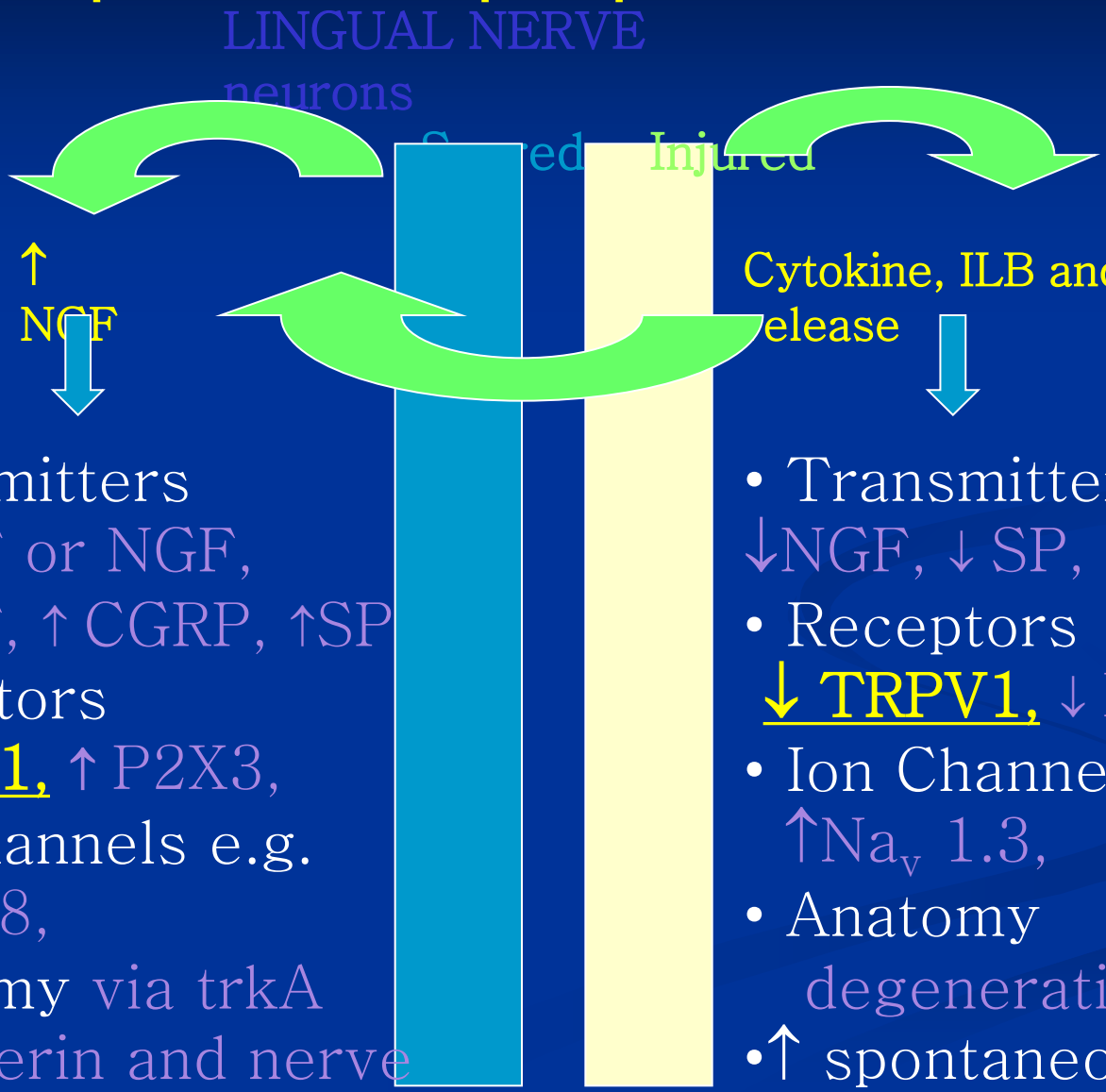
Why the lingual nerve?





- 0.5% permanent lingual nerve injury rate on removal of wisdom teeth
- 90% of injuries resolve at 10 weeks
- Routine explorative surgery at 12 weeks post injury
- Hypothesis
  - TRPV1 would be up-regulated in painful injured lingual nerve

Why TRPV1?
Consequences of peripheral nerve injury

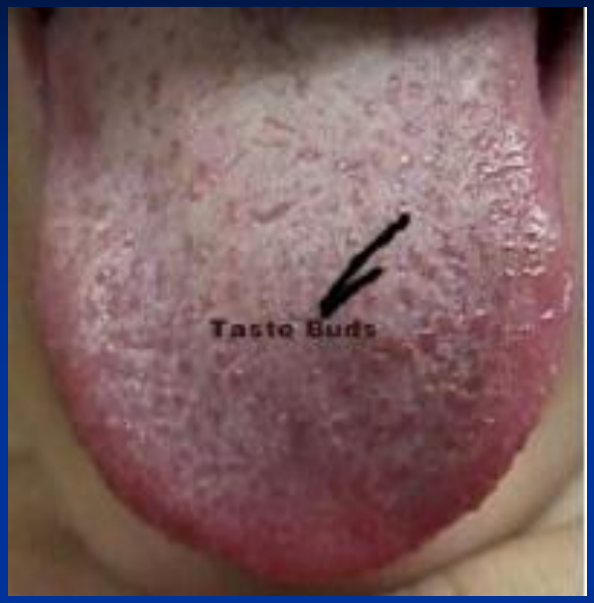


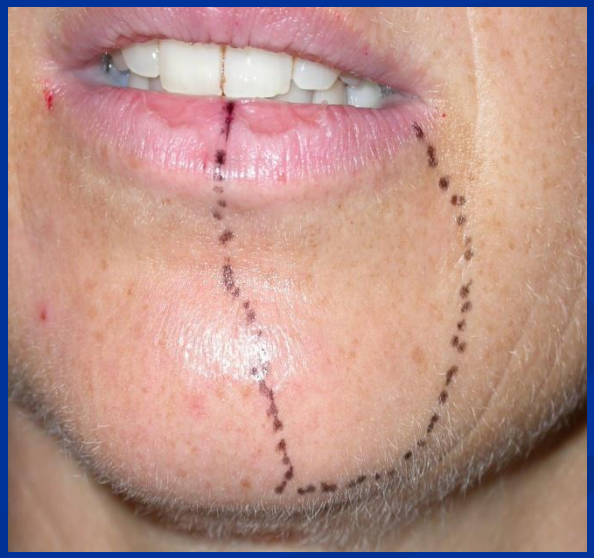
- Transmitters
↑ GDNF or NGF,
↑ BDNF, ↑ CGRP, ↑SP
- Receptors
↑ TRPV1, ↑ P2X3,
- Ion Channels e.g.
↑Nav 1.8,
- Anatomy via trkA
↑peripherin and nerve

- Transmitters
↓NGF, ↓ SP, ↓ CGRP
- Receptors
↓ TRPV1, ↓ P2X3
- Ion Channels e.g.
↑Na_v 1.3,
- Anatomy
degeneration
- ↑ spontaneous activity

Nerve injury

Lingual nerve injury	
ID block	11
Surgery	12
	23
Inferior alveolar nerve injury	
ID block	6
Surgery	8
RCT	1
Implant	12
	27





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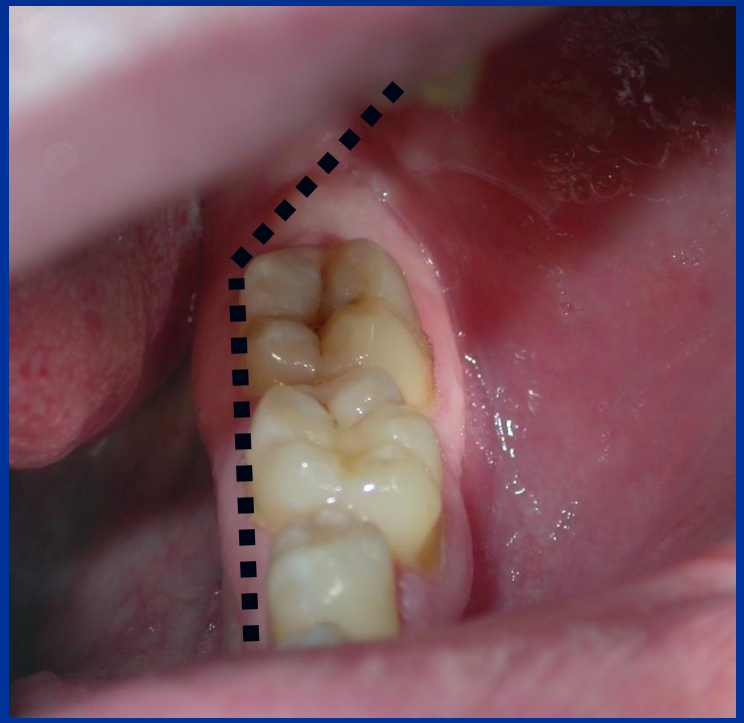
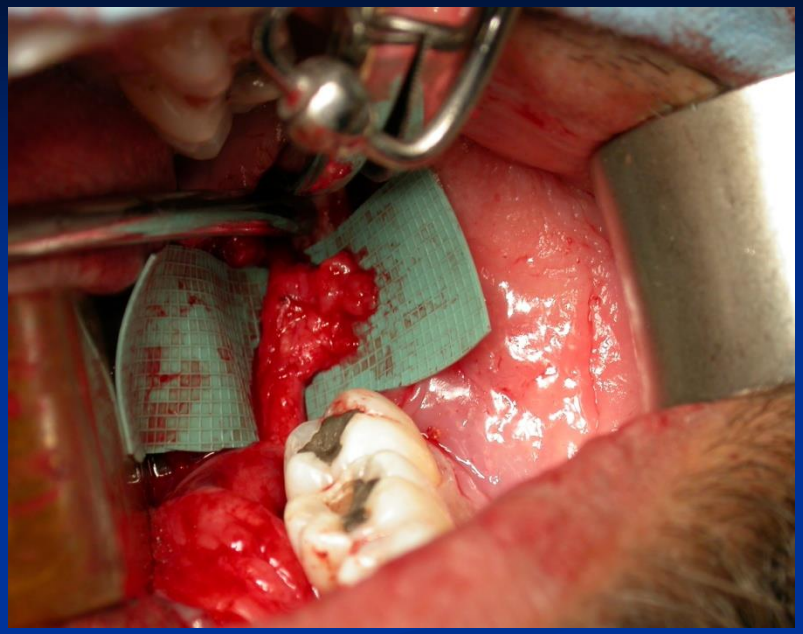
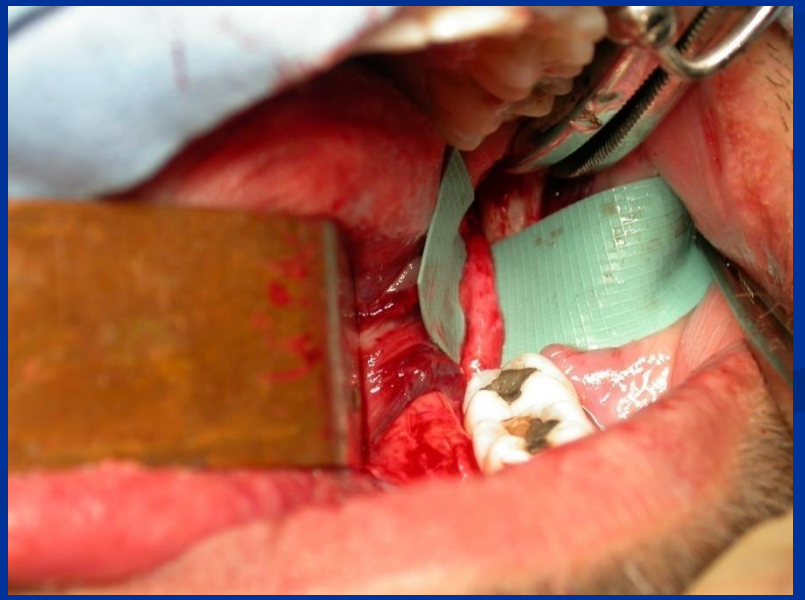
Lingual nerve

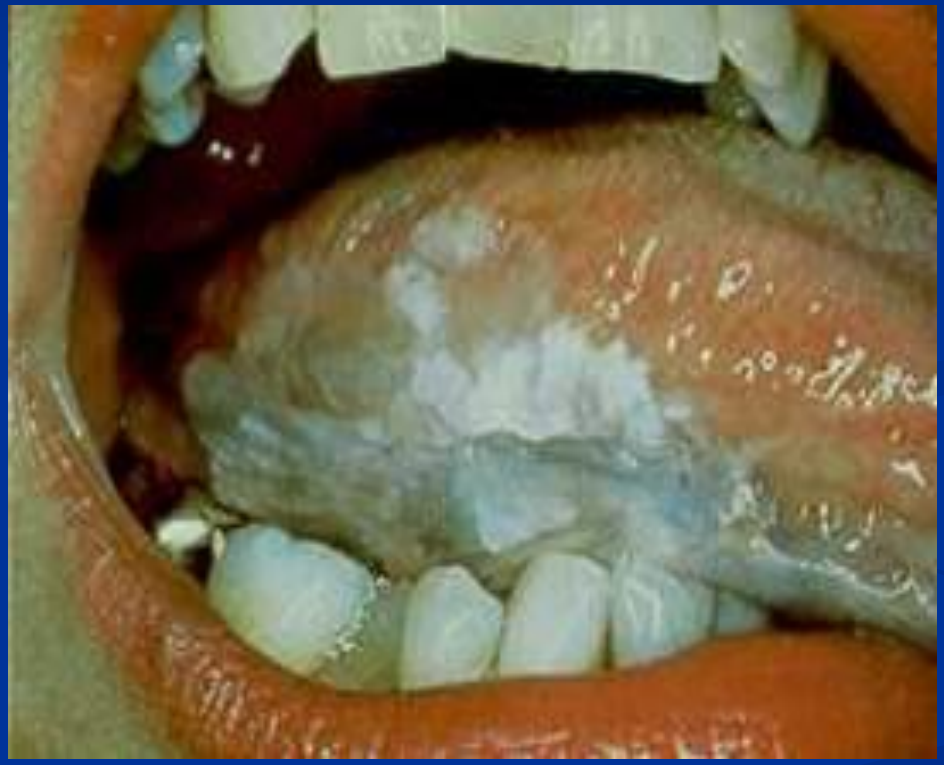
- Retromolar approach







Oral cancer excision lingual nerve control n=10



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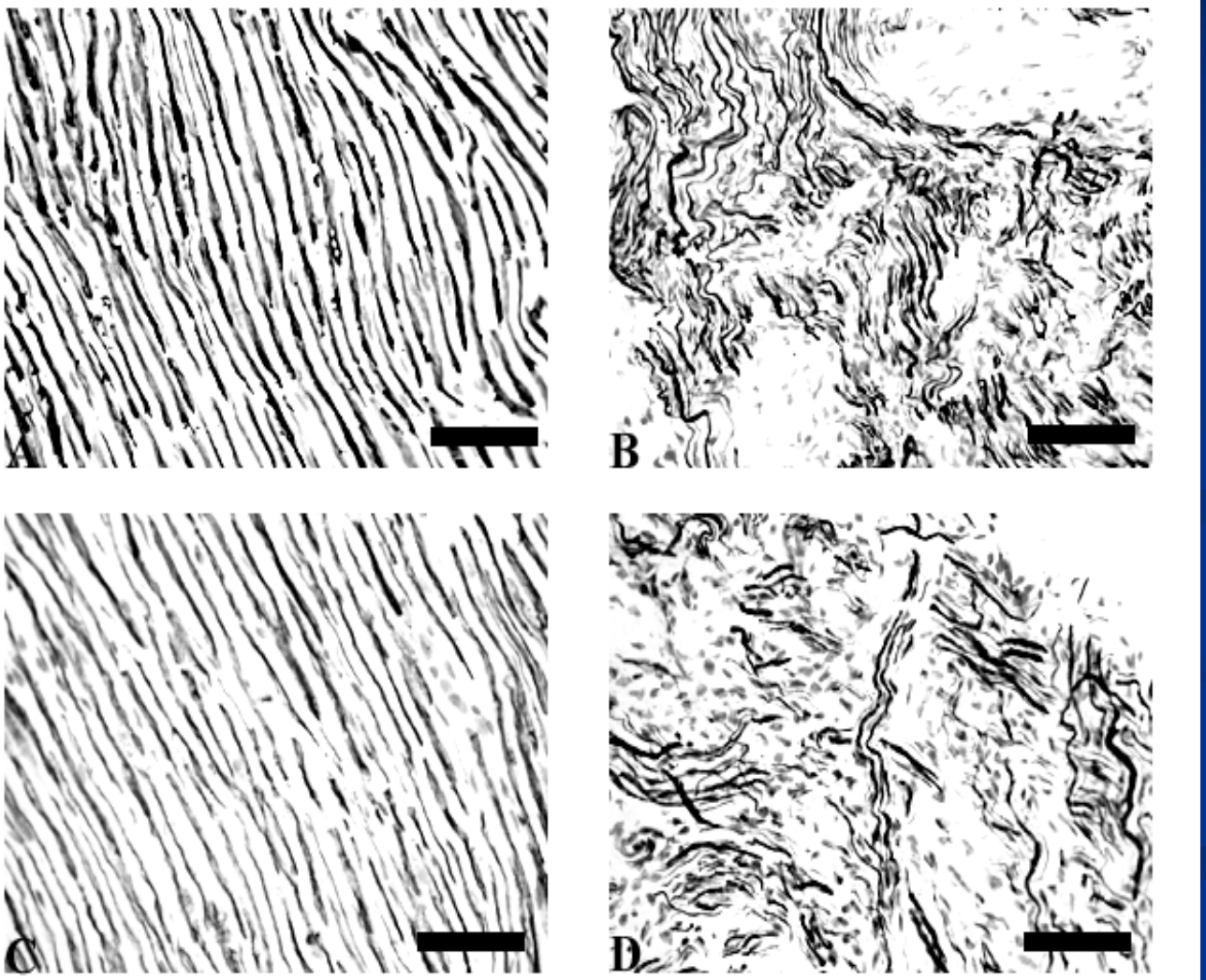
Lingual nerve Nav 1.8.

Control Injured

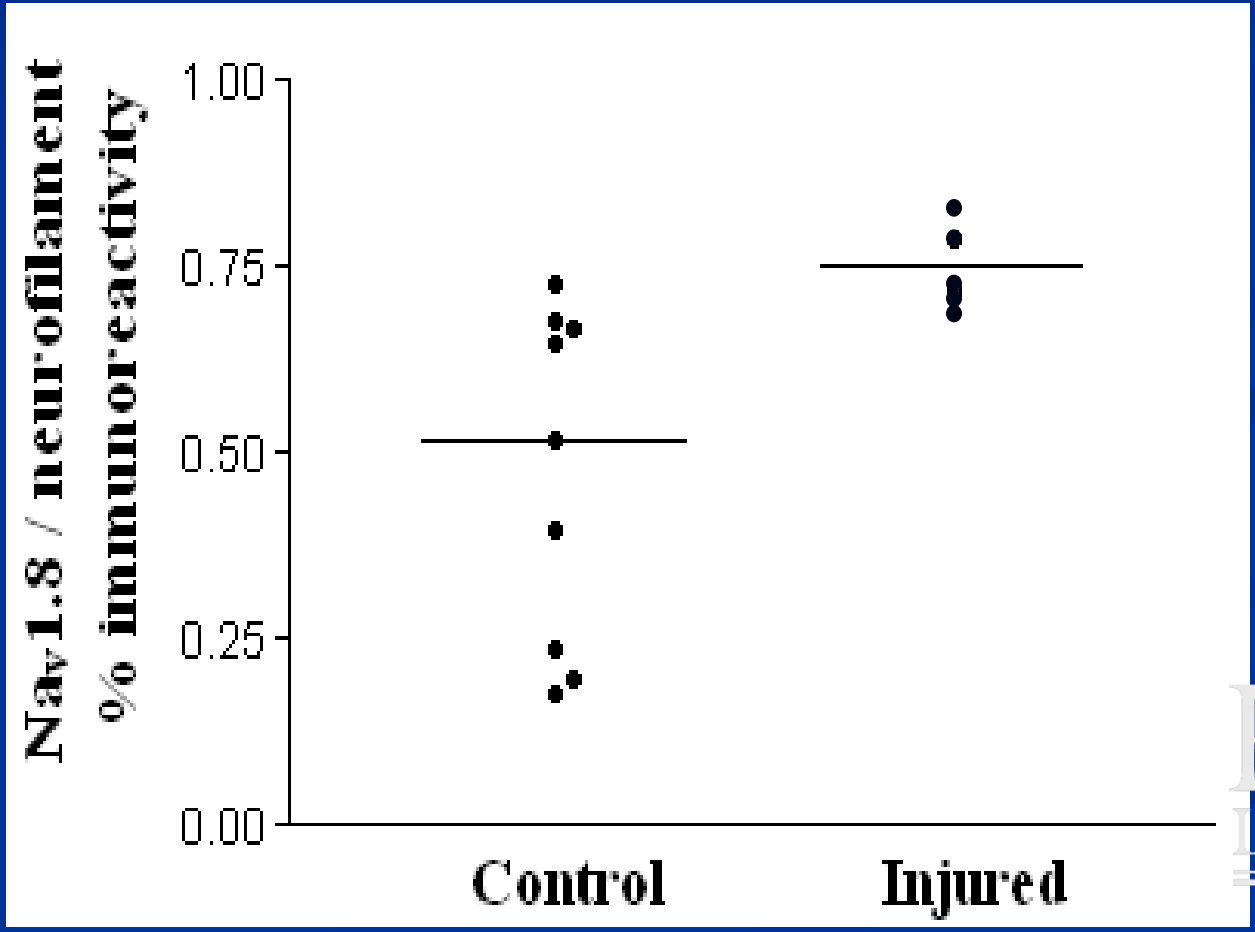
Scale bars = 50 mm

NF

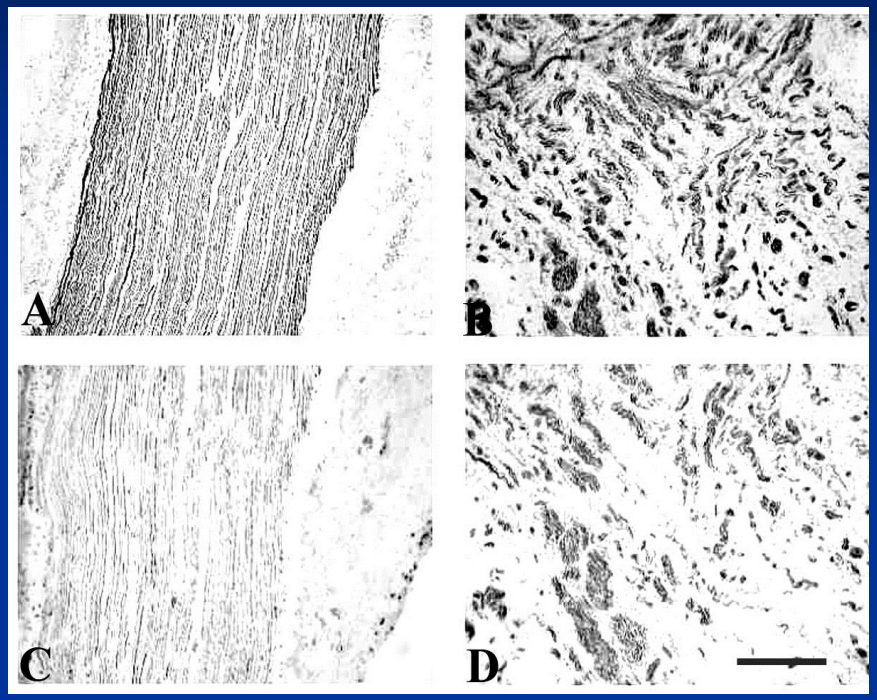
Nav 1.8

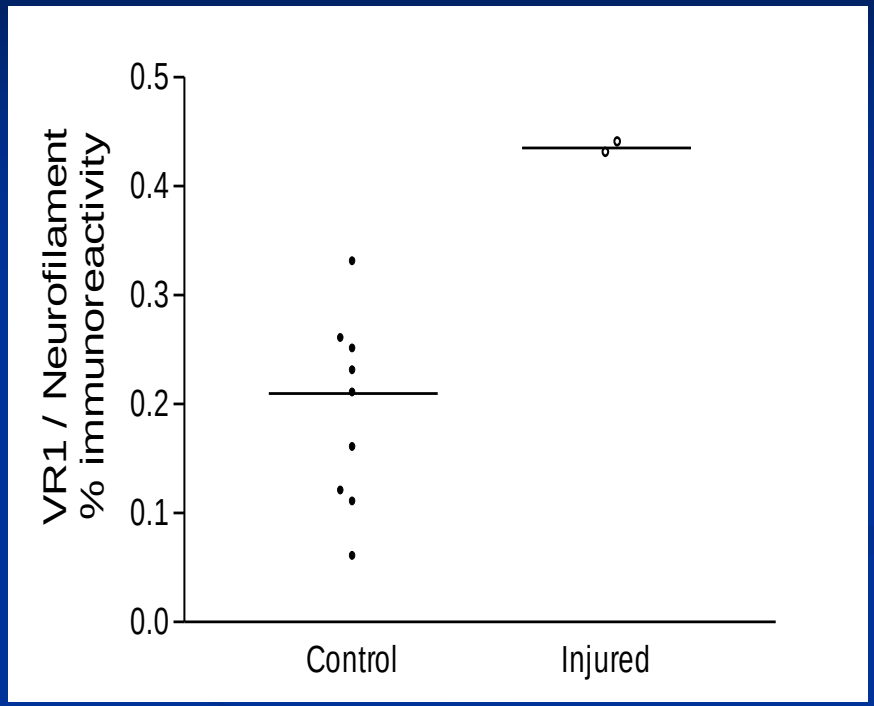


Scattergram -ratios of the percentage immunoreactive area of **Nav1.8** to neurofilament found in **lingual nerve** sections.



Lingual nerve TRPV1





Non-injured (left columns A, and C) injured lingual nerve (B and D) section
Neurofilament (A and B)
TRPV1 (C and D)
Scale bar = 50 mm.

Ratios of the percentage immunoreactive area of TRPV1 to neurofilament
The median value is indicated.* P<0.05.

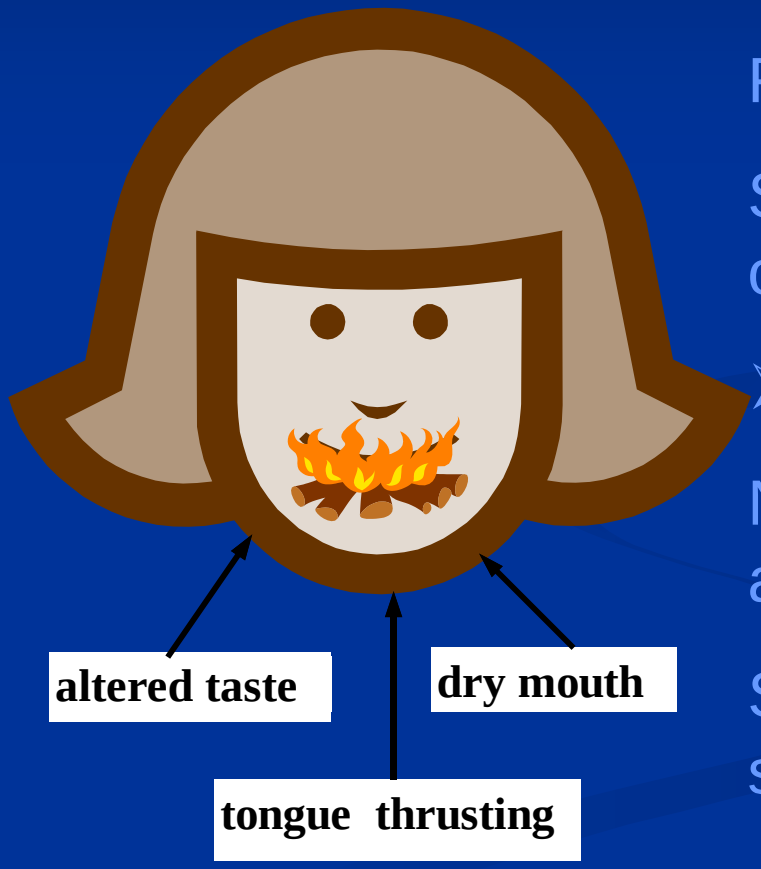
BMS

- The International Association for the Study of Pain (IASP) defines BMS as:

  'a distinctive nosological entity' characterised by 'unremitting oral burning or similar pain in the absence of detectable oral mucosal changes' that can last at least 4-6 months.

Burning Mouth Syndrome

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



Features

Spontaneous onset

➢4month duration

Normal appearance

Supertasters/taste sensitivity

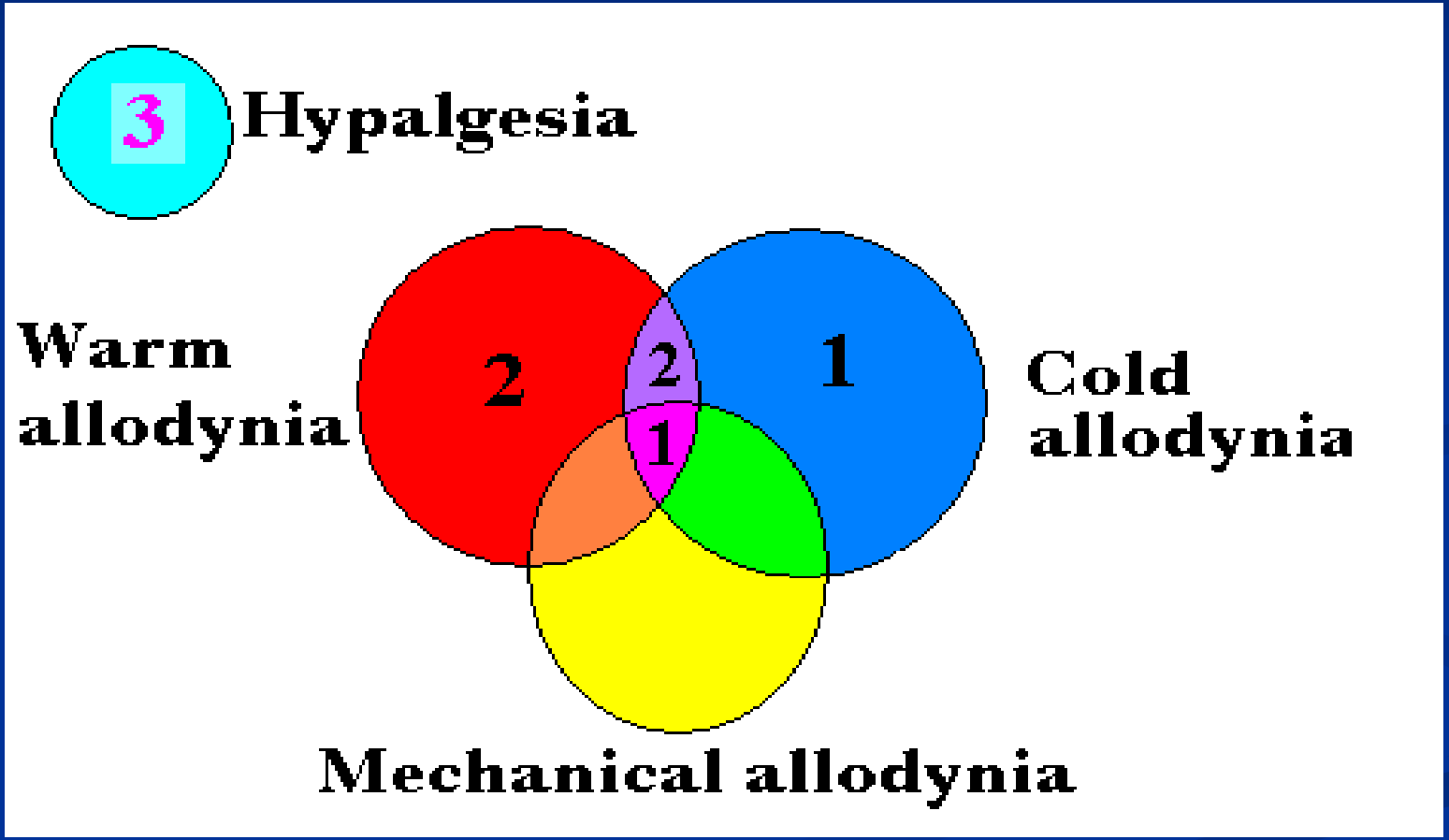
Aetiology of BMS

- An **alteration in autonomic innervation** and oral blood flow (Heckmann et al., 2001)
- Changes in endocrine status during **menopause**, causing a disruption in sensory pathways (Basker et al., 1978)
- A **disruption of central sensory** and modulatory pathways that include the spinal trigeminal nucleus and striatum (Hagelberg et al., 2003; Gao et al., 2000).
- A sensory dysfunction illustrated by changes in QST associated with a **small and/or large fibre neuropathy** (Forssell et al., 2002)
- A trigeminal, peripheral **small-fibre sensory neuropathy** (Lauria et al., 2005; Lauritano et al., 2005).

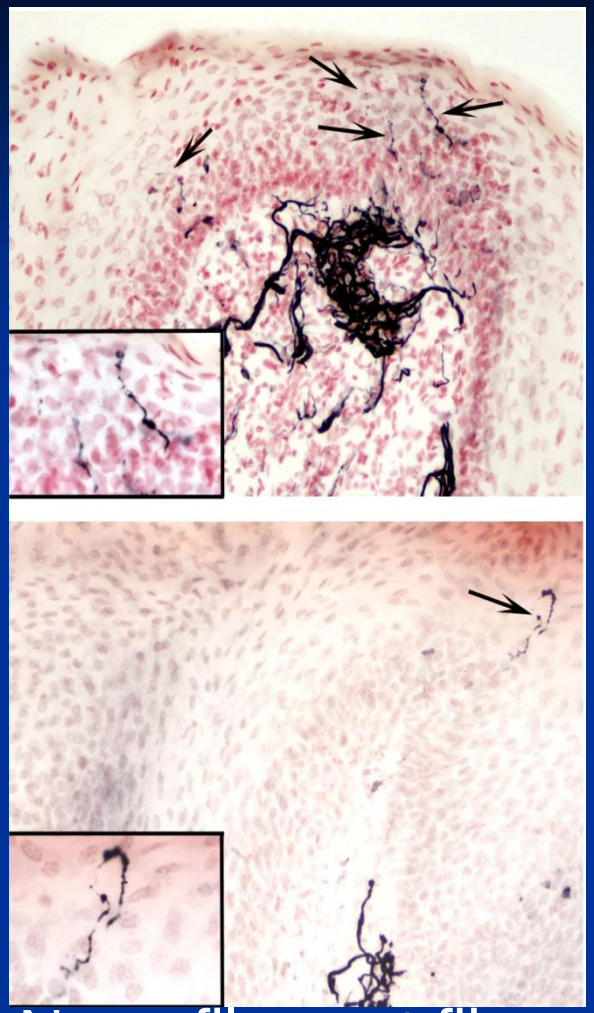
Table of reported pain

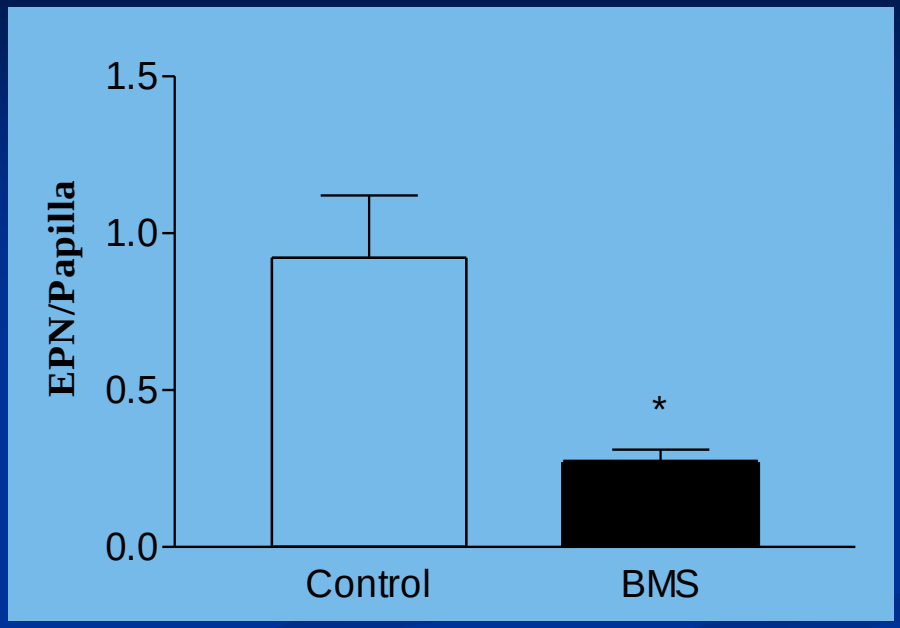
Pain:	Control N=10	BMS n=10	LNI	
			O	E
at rest	0.5±1.0	**5.3±3.1*** **	1.6±2.2	
with EC	0.8±1.2	1.4±2.3	**2.9±3.0**	
with 10 μg/ml capsaicin	0.9±1.8	**7.0±1.9*** **	**5.0±4.4**	1.0±1.7

Incidence of reported allodynia in BMS patients



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

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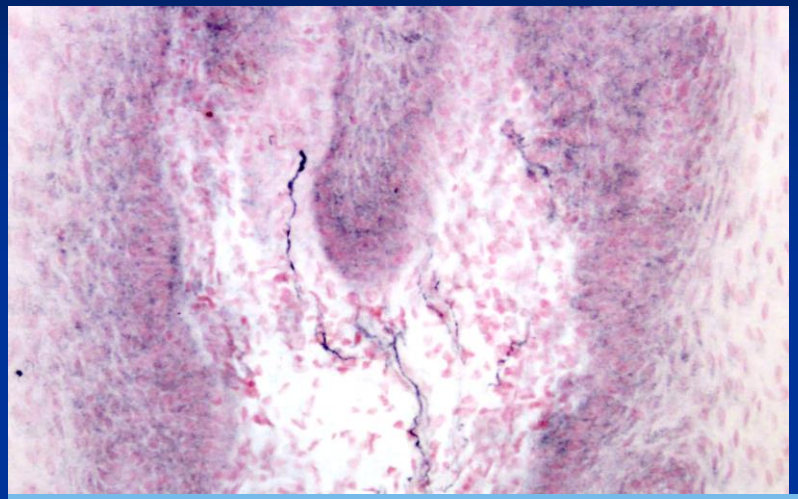
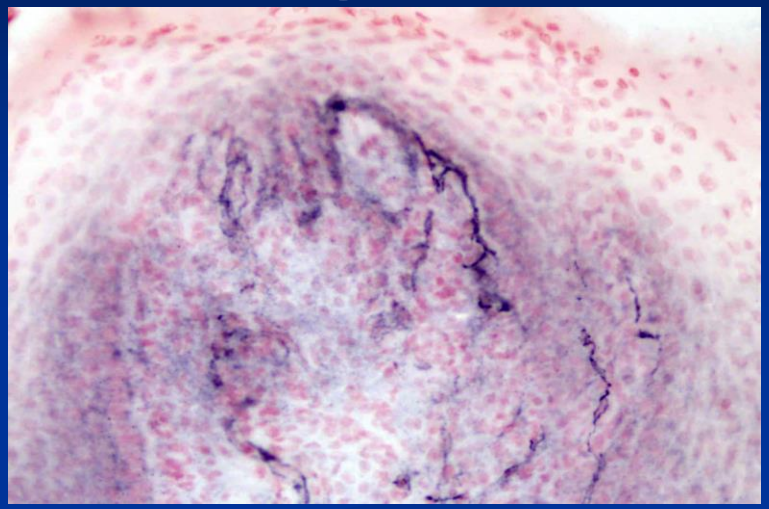
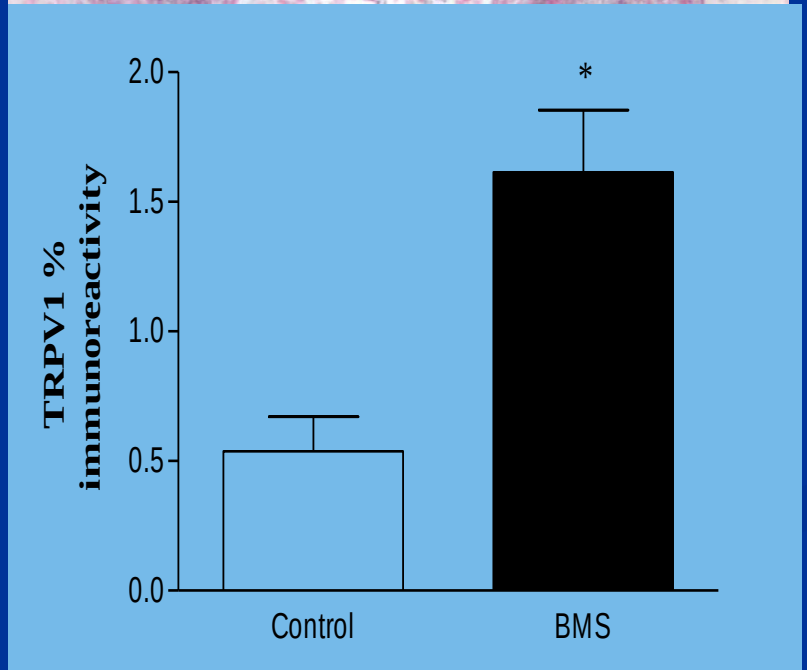
TRPV1 -IR

Control



BMS



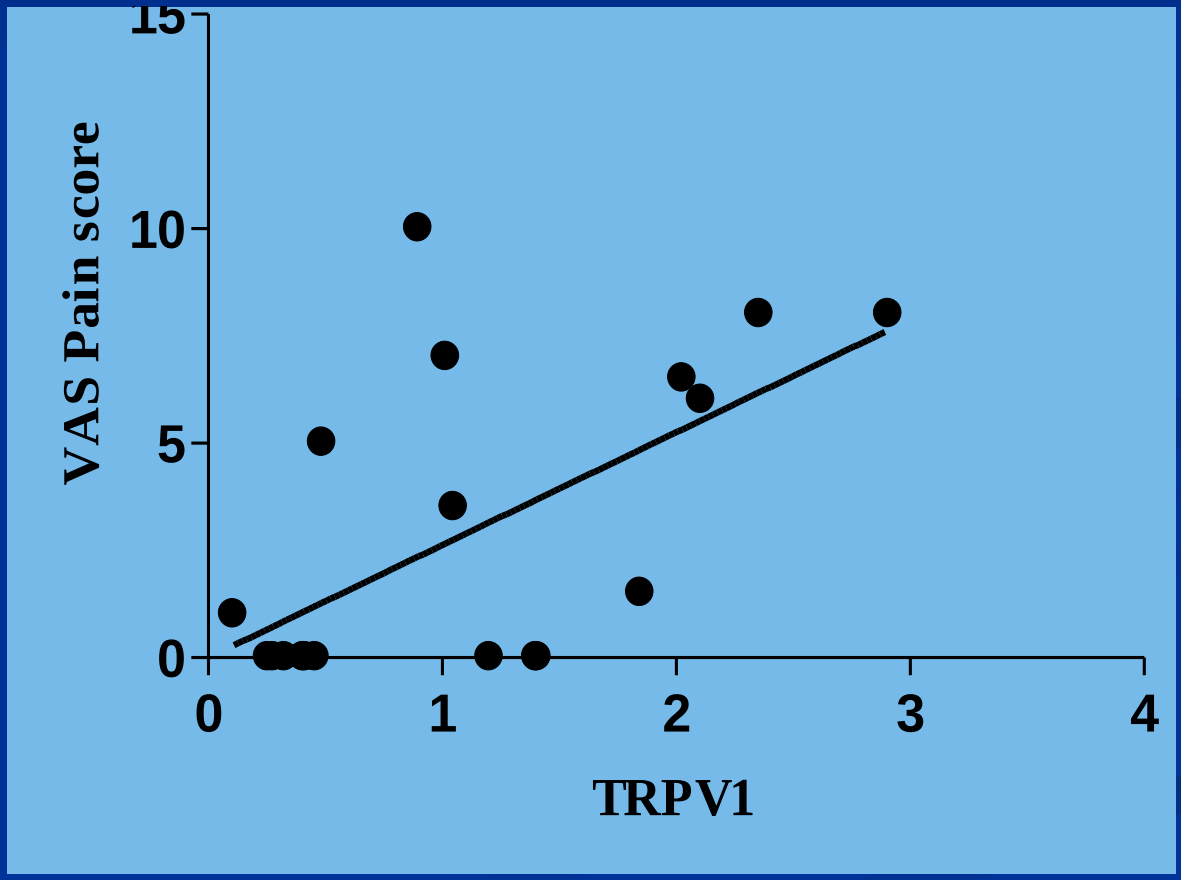


TRPV1 fibres staining in control and in BMS x20.

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



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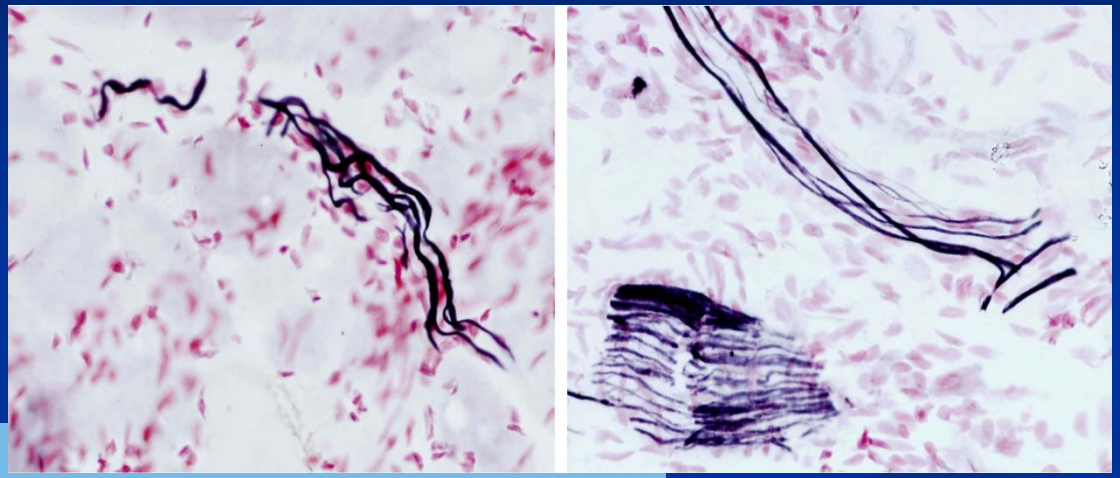
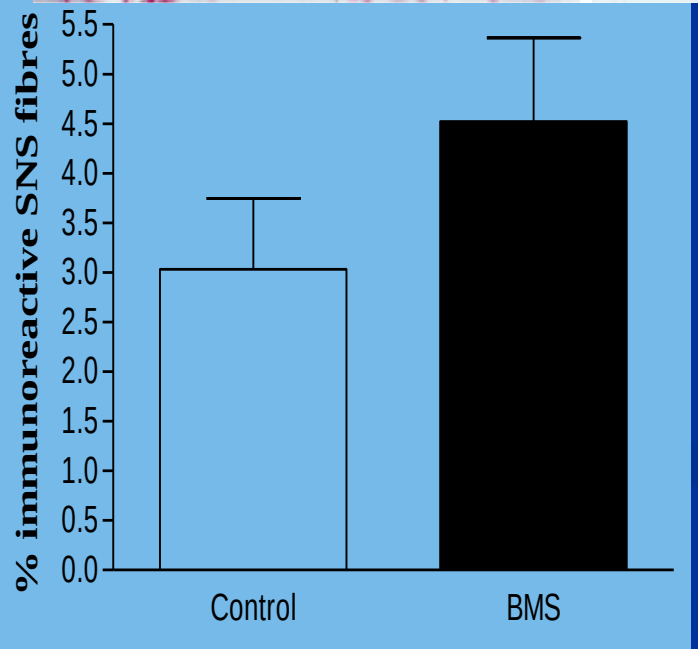
$NaV_{1.8}$ -IR

Control BMS

x40

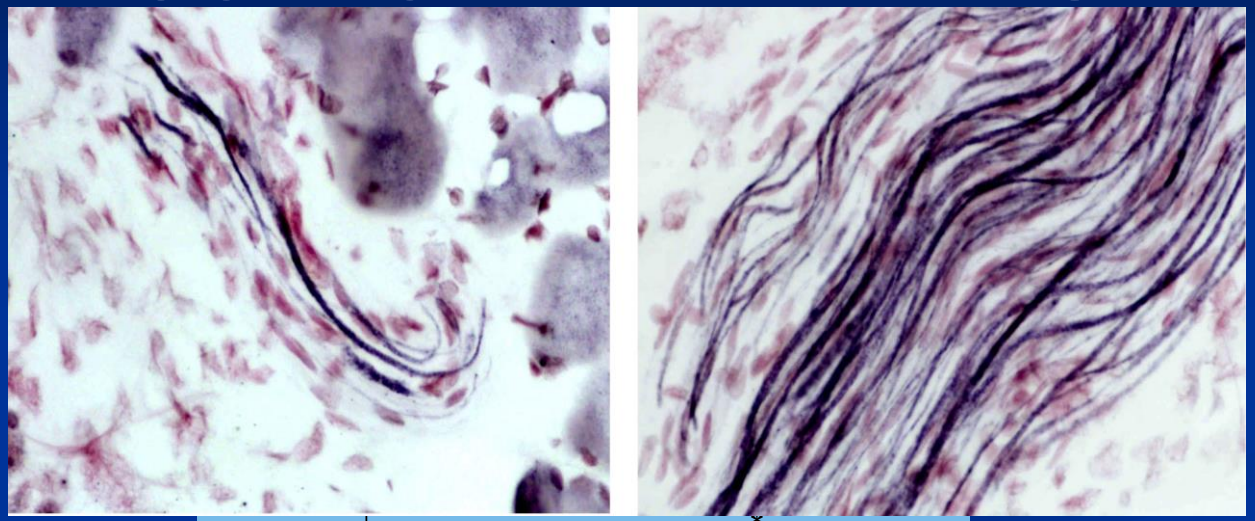




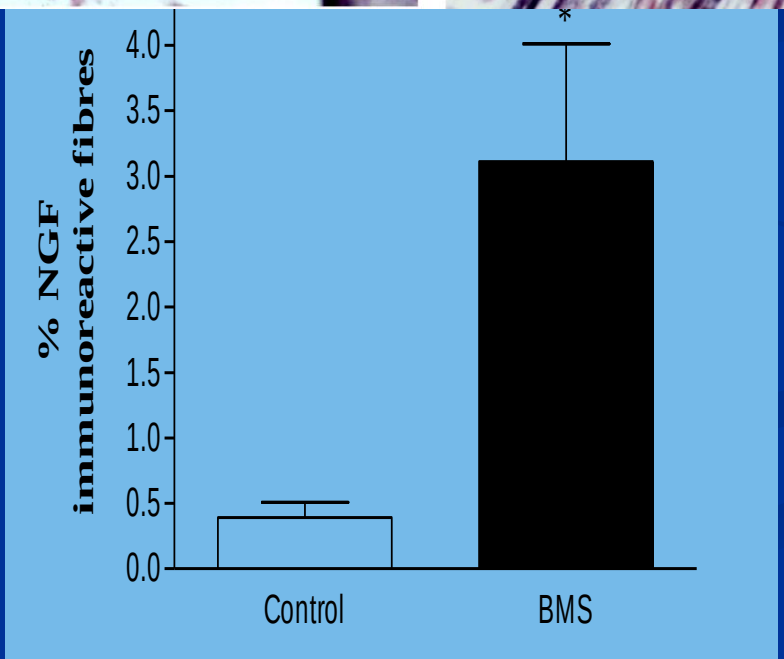
Bar chart showing the mean ± SEM of % area of NaV1.8 fibres in control and BMS tongue. = trend towards increase in Nav 1.8

NGF-IR

Control BMS



x40



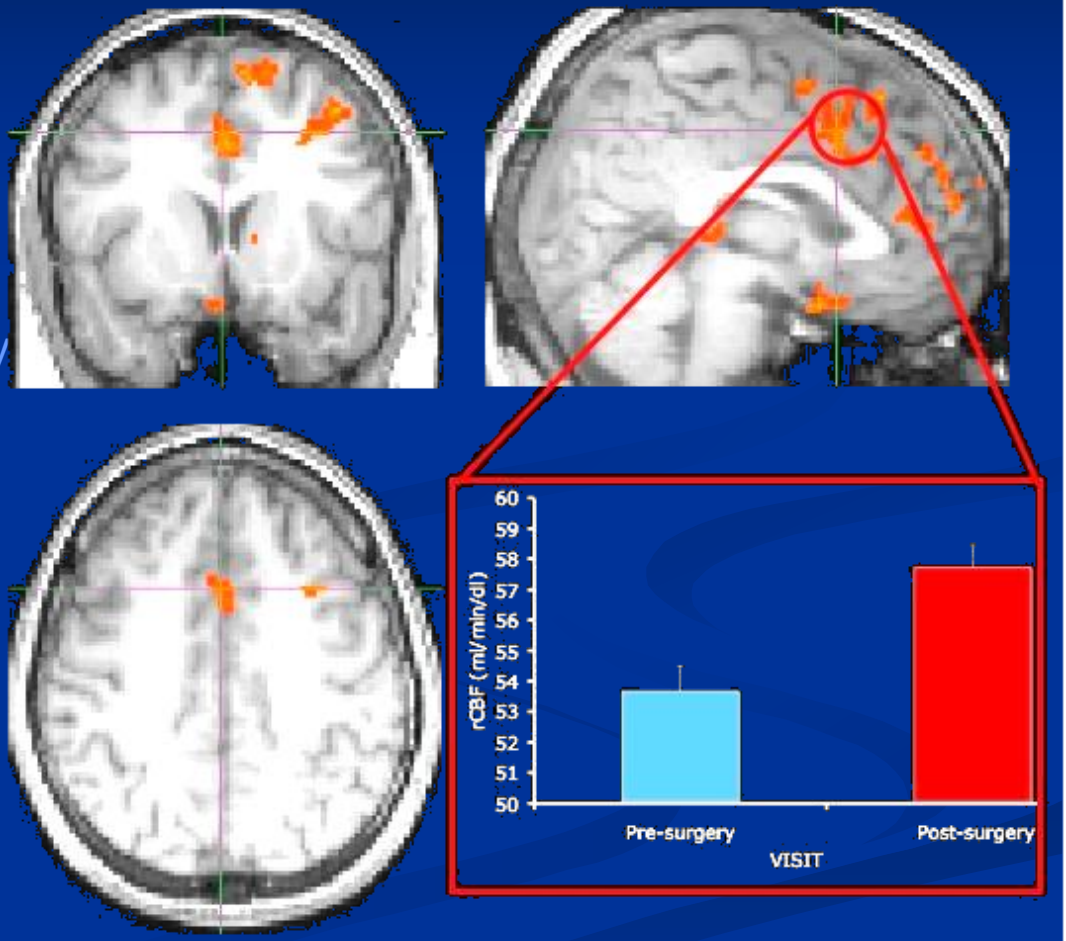
Bar charts of the mean ± SEM of % area of NGF nerve fibres in control (n=9) and BMS (n=9) tongue.
** P <0.0001*

BMS conclusions

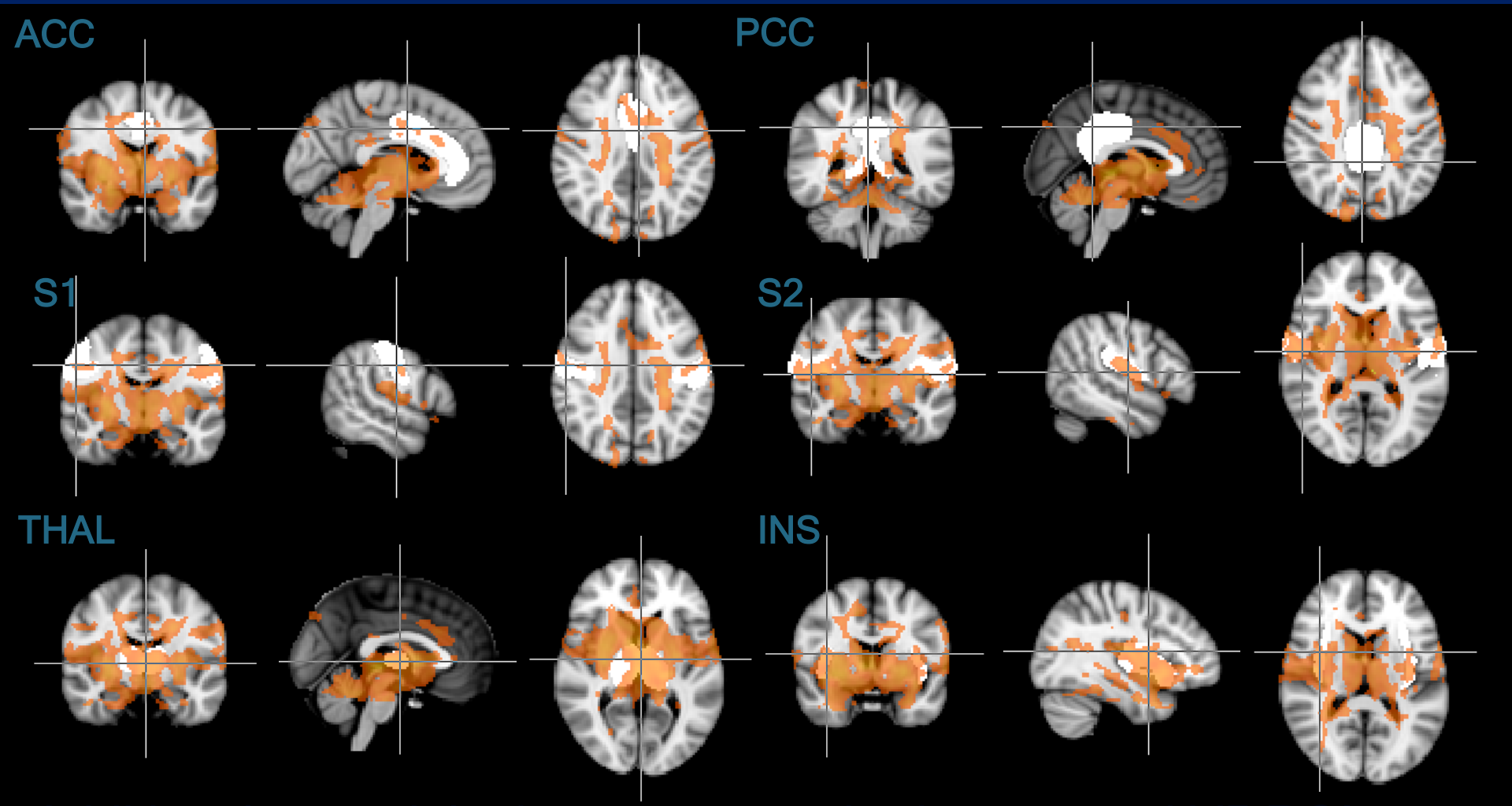
- Corroborates small fibre neuropathy with loss of intra-epidermal lingual mucosal nerve fibres.
- Increased expression of TRPV1:NF reactive fibres and NGF within NF-IR fibres
- Correlation reported pain and capsaicin allodynia with up regulation of TRPV1 and NGF
- Need to establish functional links between the TRPV1, NGF and Nav 1.8 changes and BMS
- Our findings indicate a path for increasing understanding and treatment of BMS.

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

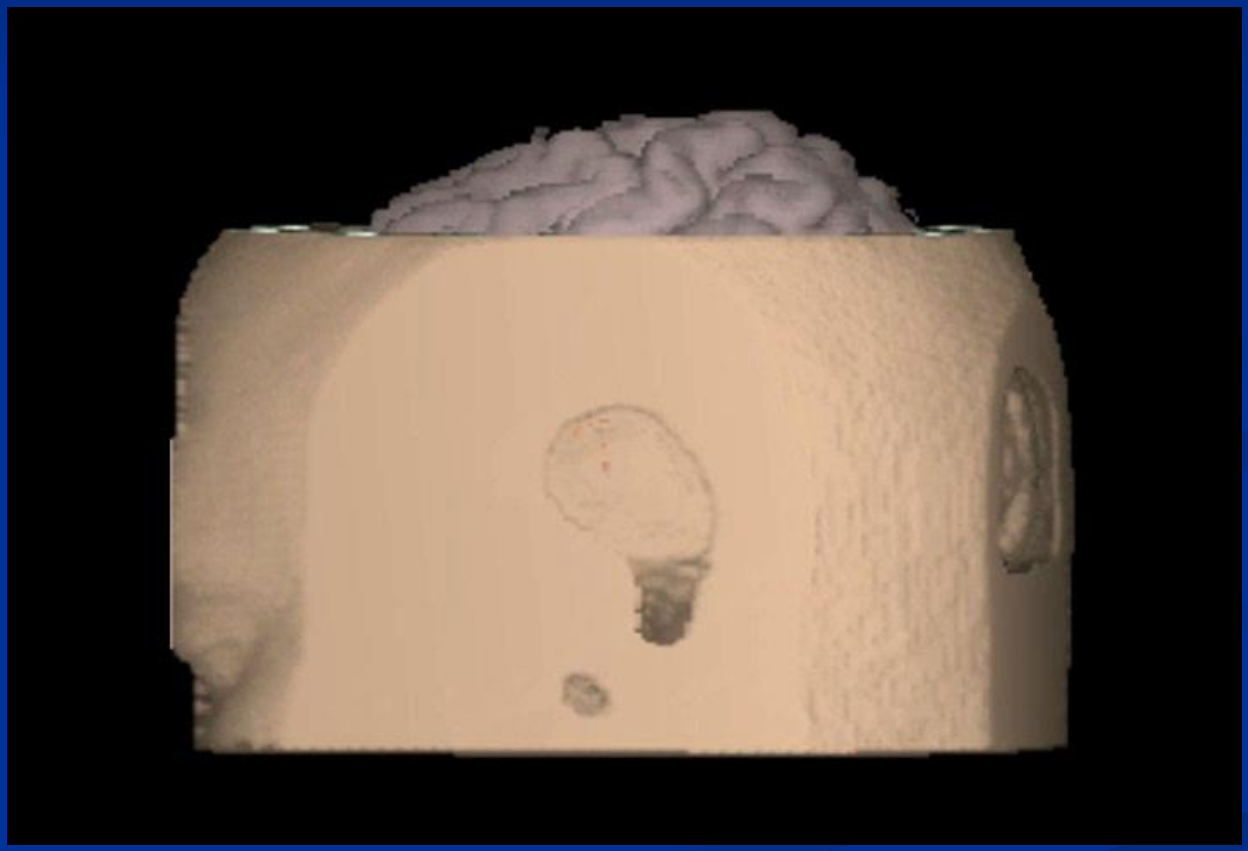


Anatomy revisited

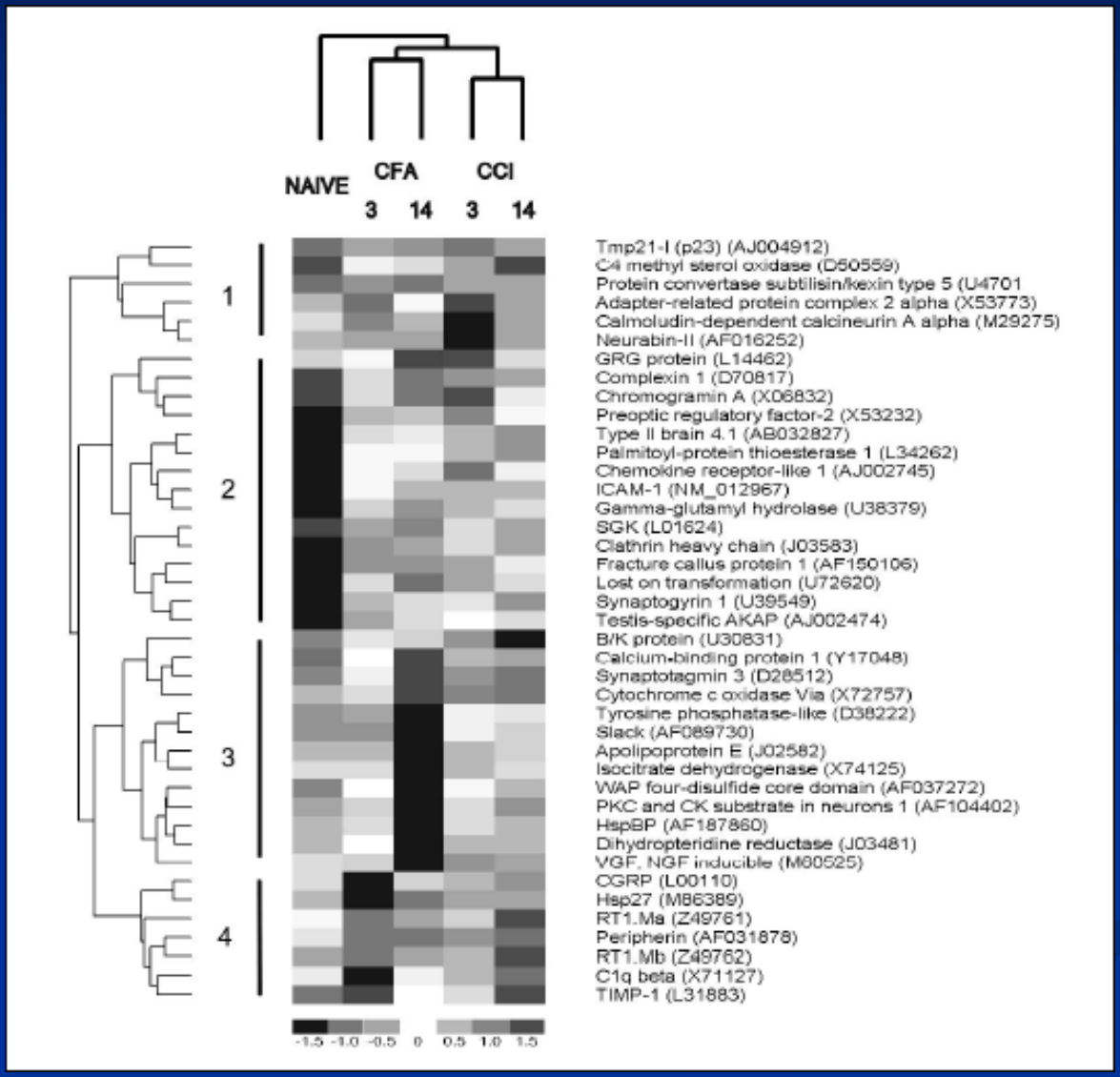


- Additional amygdala, hippocampus, brainstem, and V5 ROIs

Pain in the Brain
fMRI video

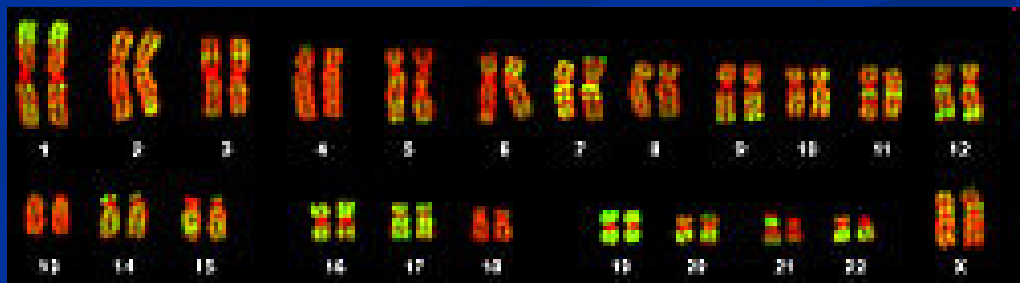


The genetic basis of V pain

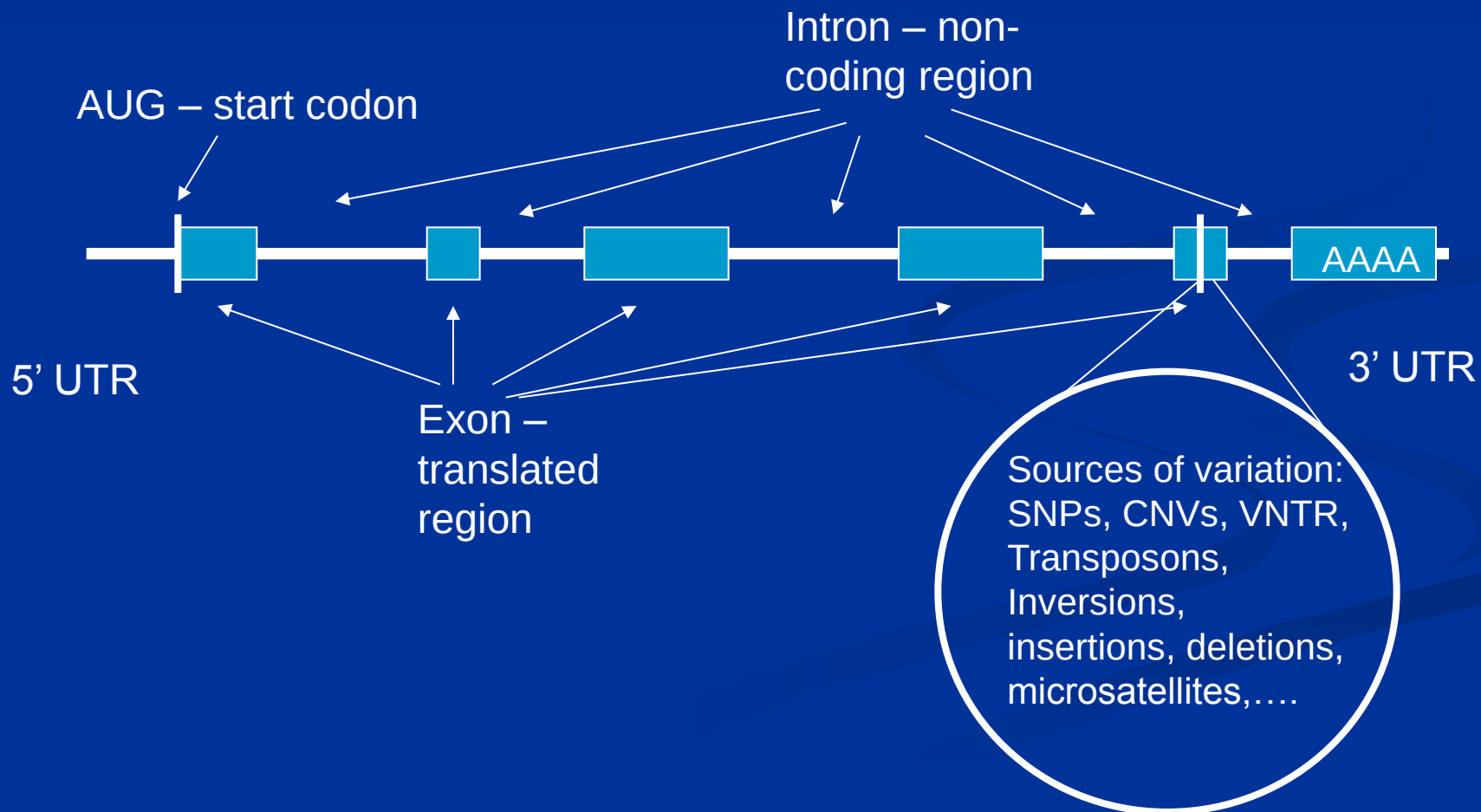


The Human Genome

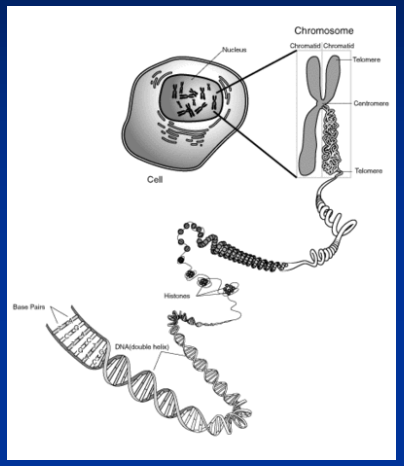
- 3.16 billion base pairs
- 23 pairs of chromosomes
- Human Genome Project has sequenced about 2.8 billion base-pairs to date
- Only 3% of the human genome actually code for proteins
- About 15% of the non-coding DNA in humans is conserved (functional importance)



Basic architecture of a gene



What genetics can do for you:



Nature

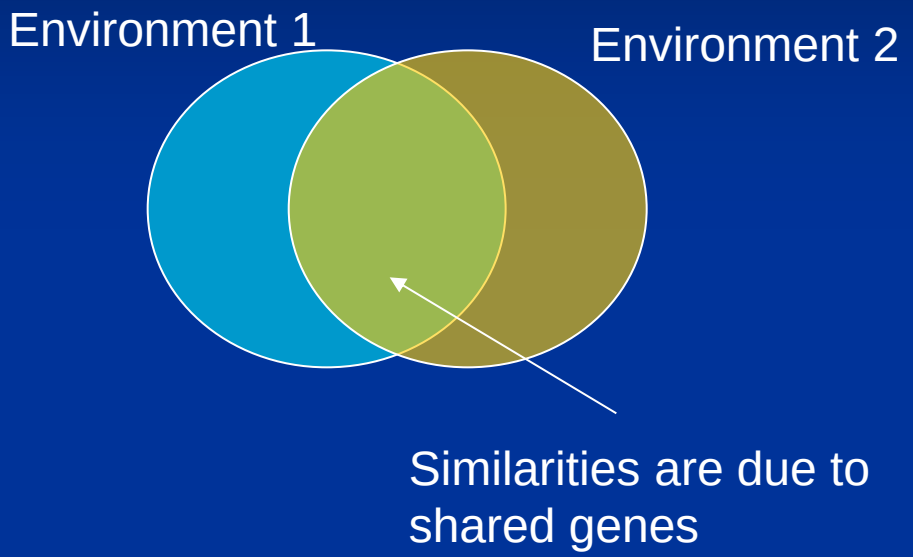
Gene-Environment Interaction

Patient

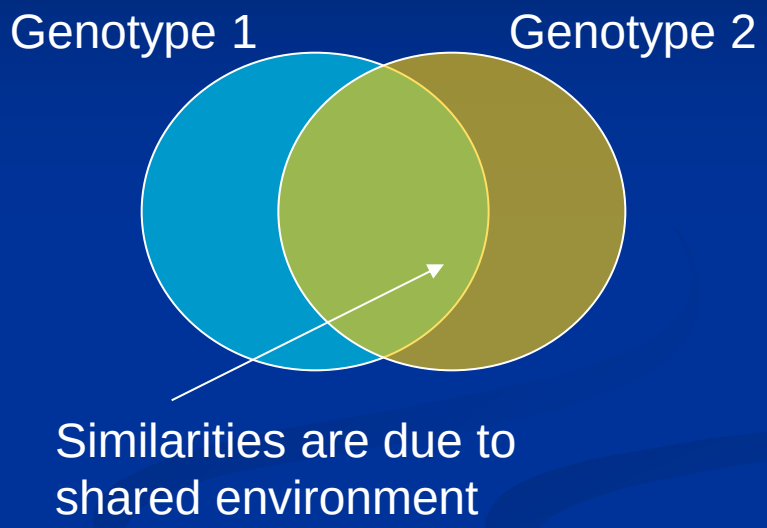
Nurture

Twin studies

Monozygous (identical) twins raised apart



Heterozygous twins raised together



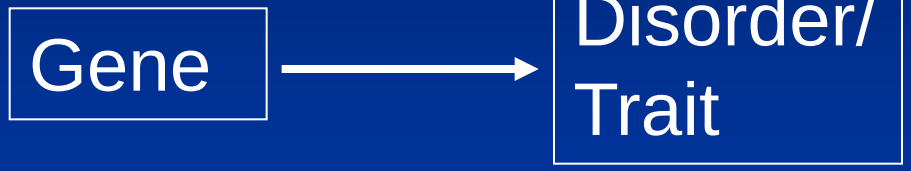
- Identify environmental causes
- Specify mechnisms of vulnerability
- Make more reliable diagnoses

Back Pain May Be In Your Genes

- The Twin Spine Study
- Researchers from Canada, Finland, the United States and the United Kingdom compared identical twin siblings who differed greatly in their exposure to a suspected risk factor for back problems;
- for example, one of the twins had a sedentary job while the other had heavy occupational physical demands, or one routinely engaged in occupational driving while the other did not.
- The studies yielded startling results, suggesting that genetics play a much larger role in disc degeneration than previously thought.

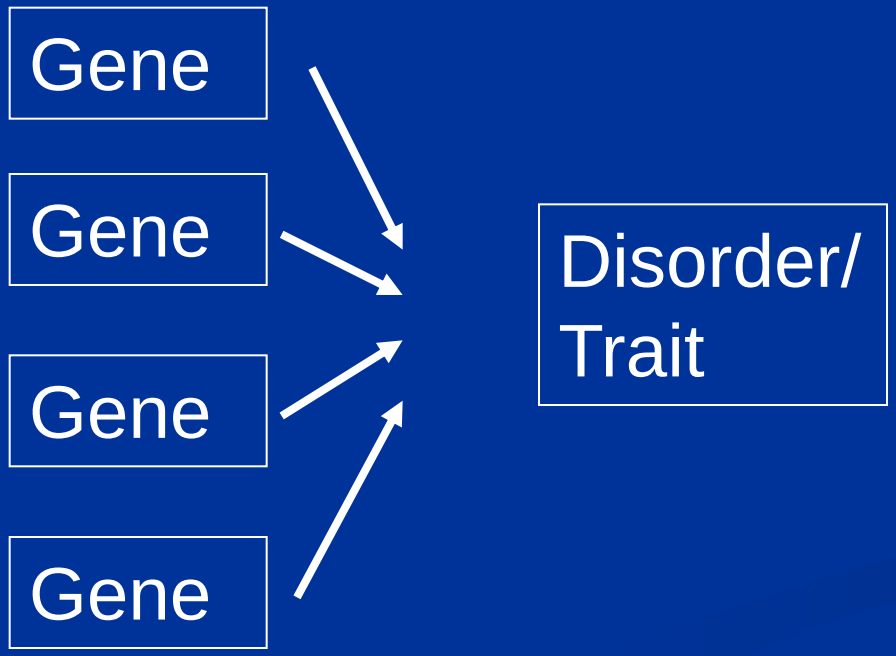
Genetic architecture

One Mutation One Disorder



Examples: congenital insensitivity to pain + SCN 6, ...

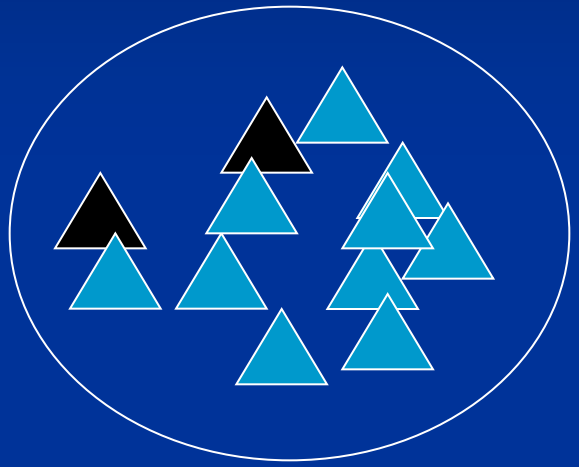
Quantitative Trait Loci



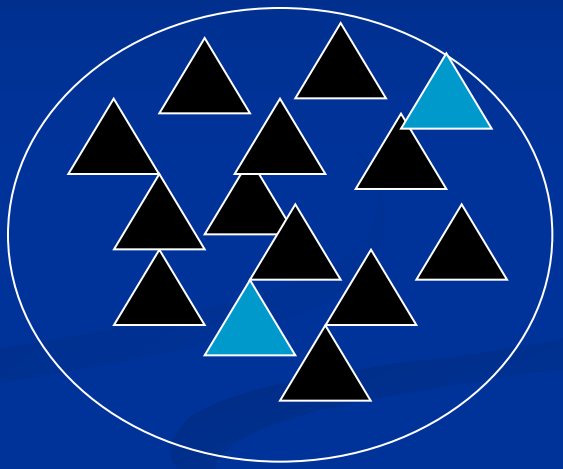
Examples: Pain sensitivity, Pain thresholds ...

Case/Control-Analysis

Controls



Cases



The difference in phenotype is due to the difference in genotype.

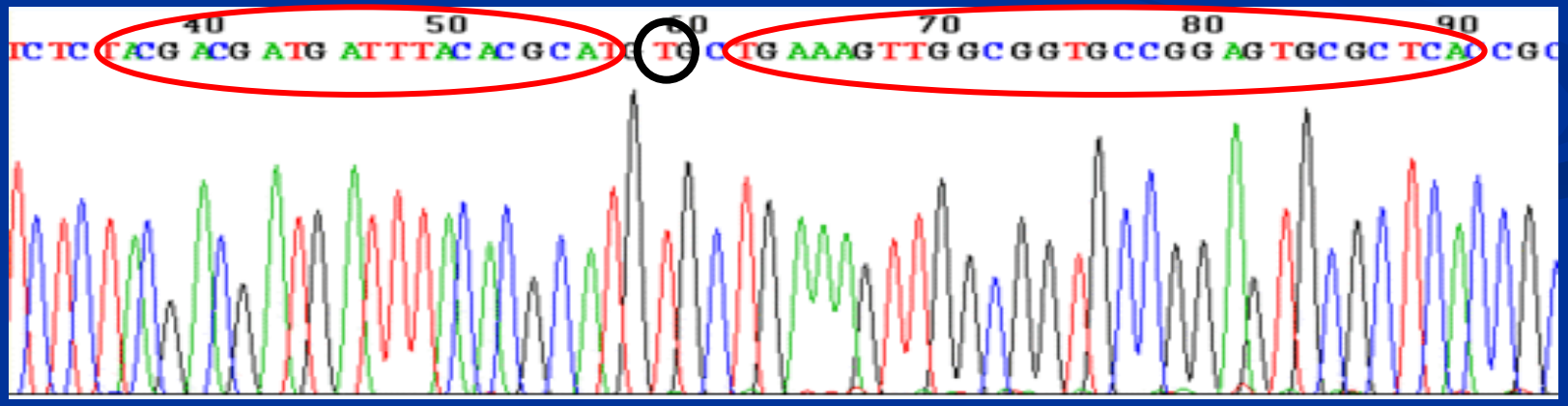
Genotyping vs. Sequencing

1. Which combination of alleles (AA, AT or TT) does the person carry in this position?
2. Is it associated with the phenotype of interest? Do I find it more frequently in cases than controls?

rs8063685 *[Homo sapiens]*

ATTAGTACCTCTGAATTAGAACACAT[A/T]ATATCGTGGAAGTGTCACAGTTGGA

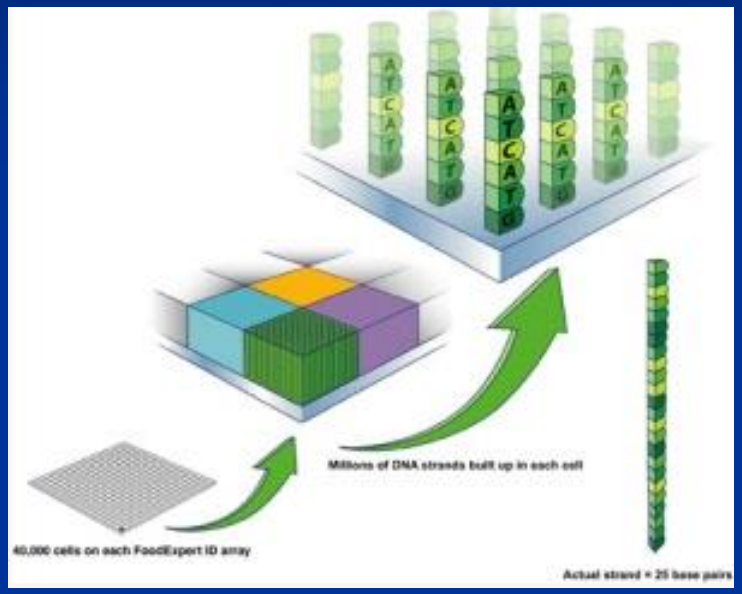
1. Which base-pairs does the person carry in my targeted region (e.g. gene)?
2. Which of them are associated with my phenotype of interest?

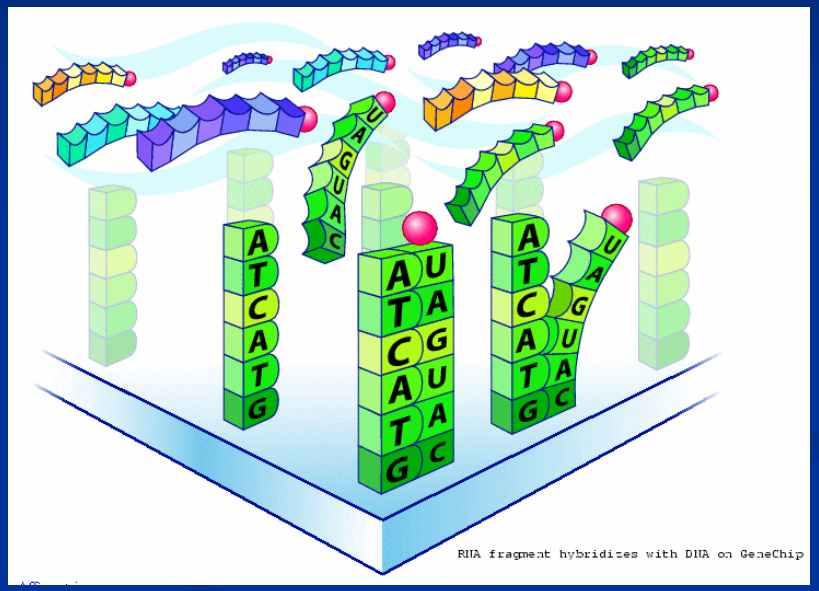


METHODS: How do we find them?

- Blood/tissue samples are obtained from patients and controls
- DNA / RNA is isolated
- DNA/ RNA is processed using
  - Genotyping
  - Seqeuencing
  - Microarrays
  - Methylation and histone modification studies
- Results are statistically analysed

How arrays work



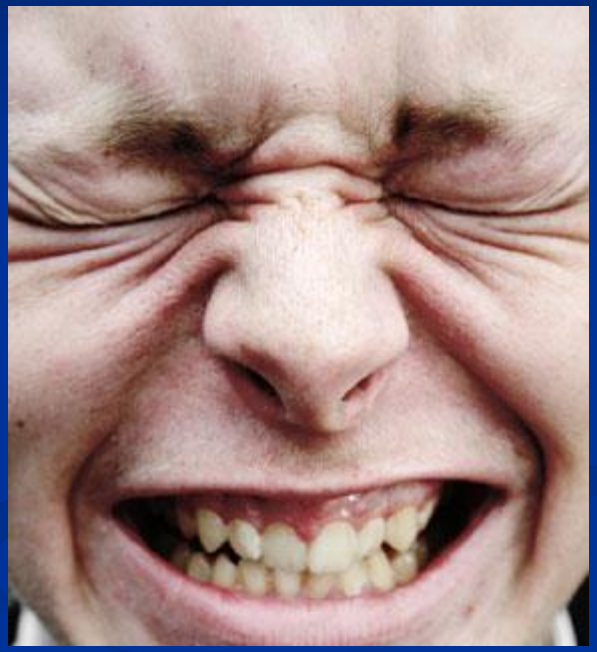


An array or chip consists of up to 1,000,000 probes of different DNA nucleotide sequences

In the hybridisation step the (c)DNA strands are washed over the array surface and connect to the complementary strands.

The genetic basis of V pain

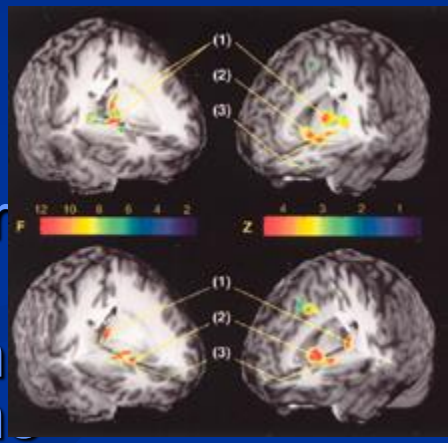
- "Human genetics has showed us how the risk of pain is reduced naturally. Now we need drugs that convert unfortunate pain-sensitive people into fortunate pain-insensitive individuals. The right drugs might reduce both postsurgical pain and prevent the establishment of chronic pain," Woolf says.
- GCH1 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 and don't know when they're harming themselves.
- Although capable of feeling other sensations like warm and cold, their lack of pain perception have put them in harm's way.
  - 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

- 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.
- By combining genetic testing with molecular brain imaging techniques and controlled and sustained jaw pain
- The COMT enzyme helps govern aspects of brain chemistry involving the neurotransmitter chemicals dopamine and noradrenaline.
- The gene that encodes it occurs commonly in two forms, or alleles, which make copies of the enzyme that are different only by one amino acid, either valine (less pain) or methionine.
- 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.



Genetics of pain

- Red heads have more pain
- Melanocortin 1 receptor def
- 20% increase pain

Genetics of pain

- Approximately 25,000 genes in the human genome How many genes are involved in pain mediation ?
- Sodium ion channels
  - SCN1A discovered to cause of familial hemiplegic migraine (FHM).
  - SCN9A in neuropathic pain as well as in inability to experience pain
- GTP cyclohydrolase (GCH1)
  - modulating sensitivity to pain in normal individuals and modulating liability to chronic pain.
- Catechol-O-methyltransferase (COMT) and the cytochrome P450 variant allele CYP3A5
  - modulate the genetic response to opioid medications in humans

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) where

The future of pain genetics

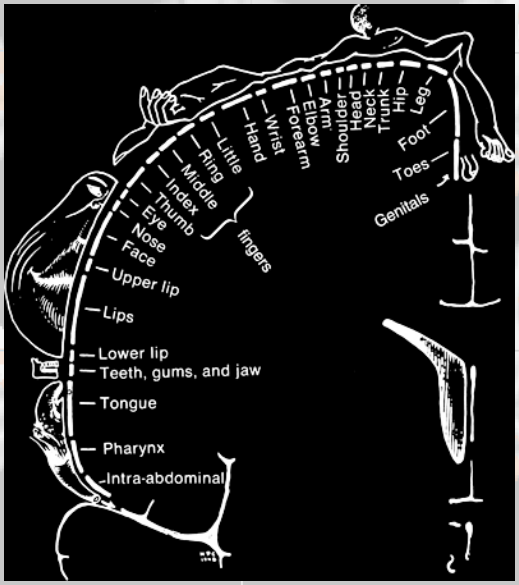
- Improved diagnostics and patient care (e.g. „customised“ medication (CYP2 D6), side effect reduction, risk management)
- Cost of genetic analyses will decrease, respectively more genotyping will get done for the same costs
- More information will be available on biological functions of genes and proteins
- Increased interdisciplinary work (imaging genomics, proteomics, QST,)
- Epigenetics will receive increased attention
- Increasing numbers of papers on pain genetics

Thank you

Anatomy revisited

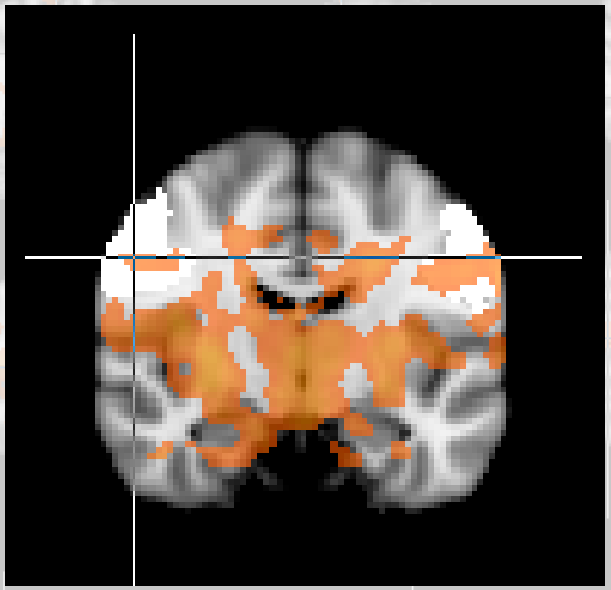
ACC

PCC



S1

S2



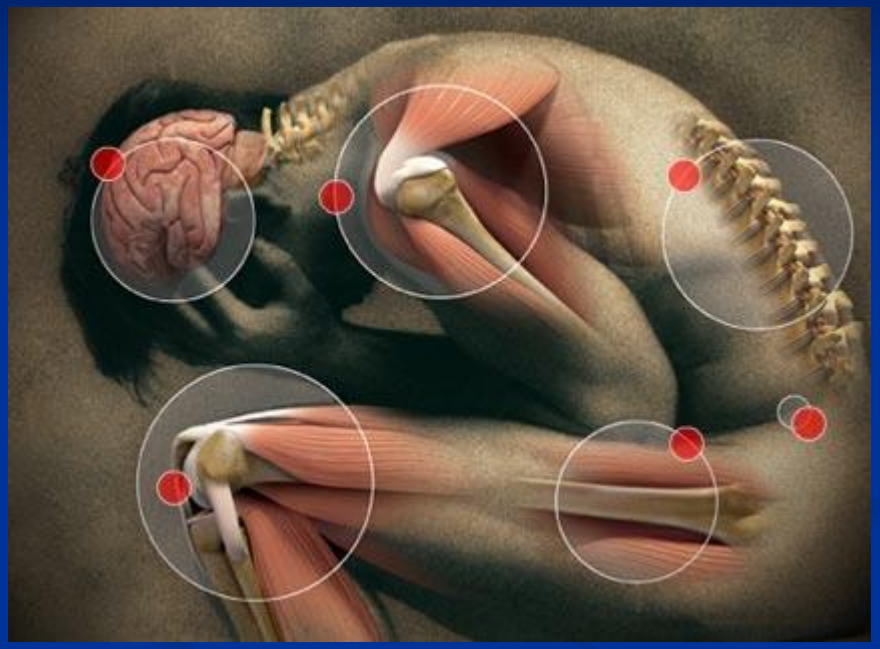
THAL

INS

- 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.

- 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.

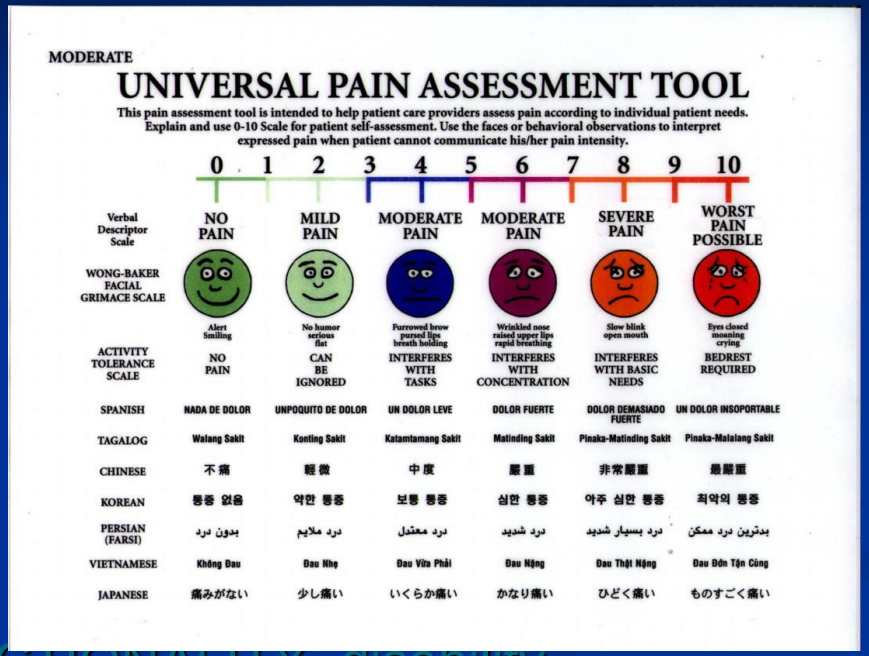
Pain assessment



- 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

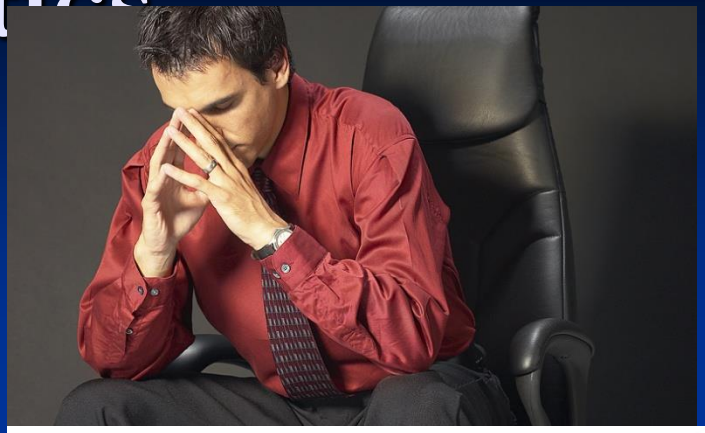


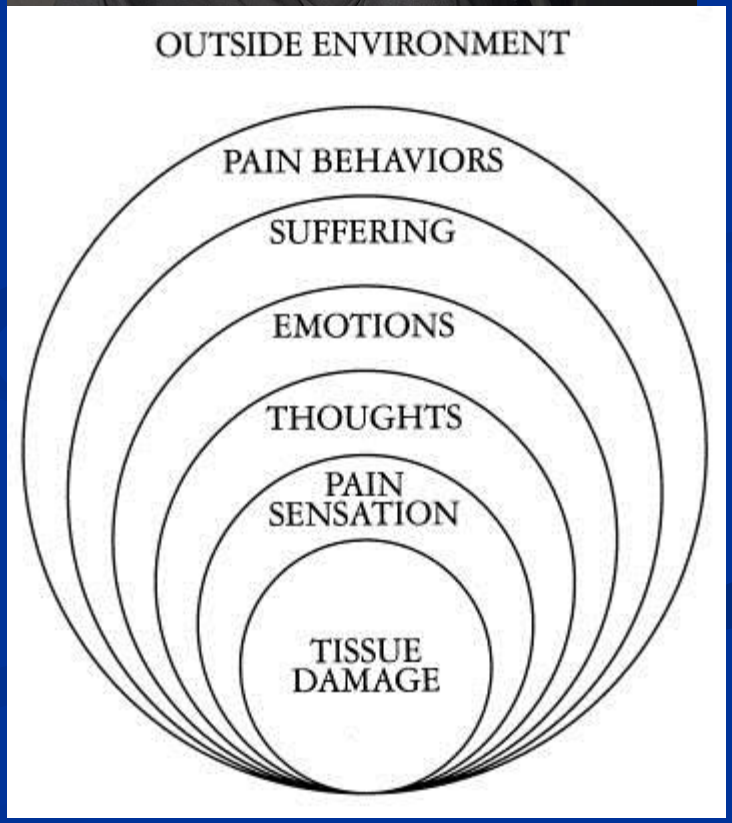
Pain history

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

Psychometrics

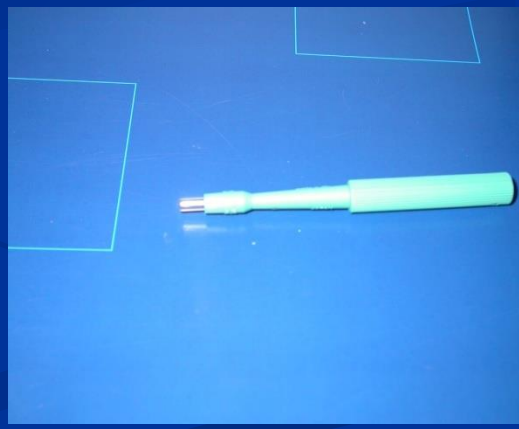
- Measure
  - Affective
    - Anxiety
    - Depression
    - Beliefs
    - Fear
    - Anger
    - Coping





Assessment - neuropathy

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



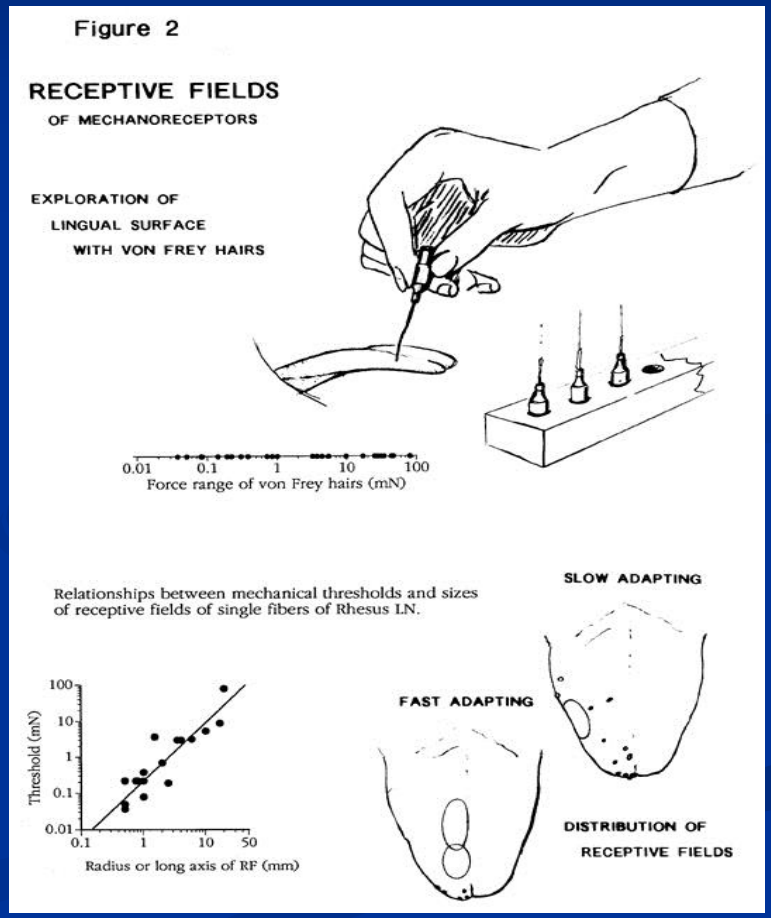
What are the problems?

With current assessment of trigeminal function

Solely mechanosensory (large fibres only)

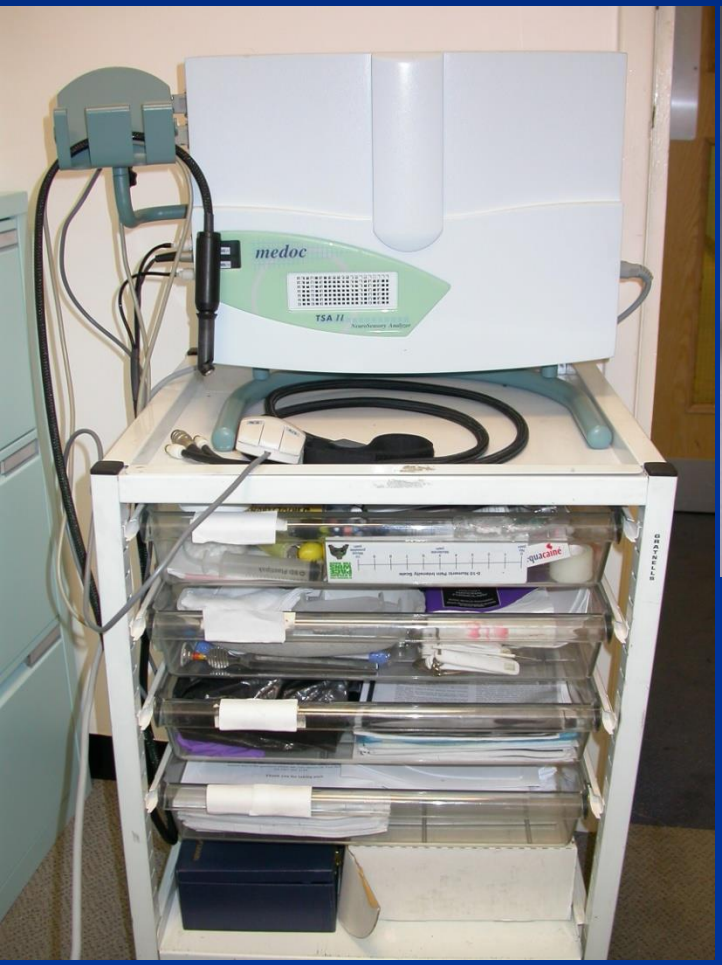
Taste tests unreliable

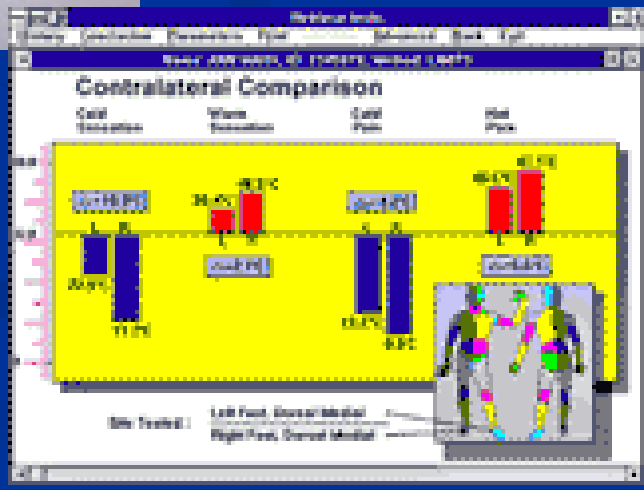
Pain and altered sensation often over looked



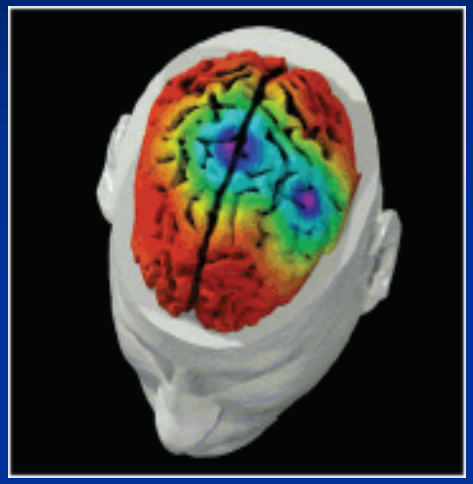
Psycho physical testing

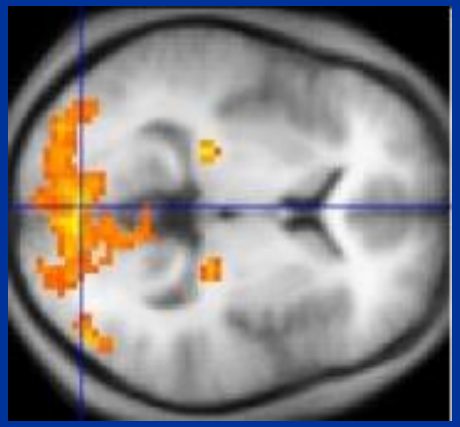
Quantitative thermo sensory testing

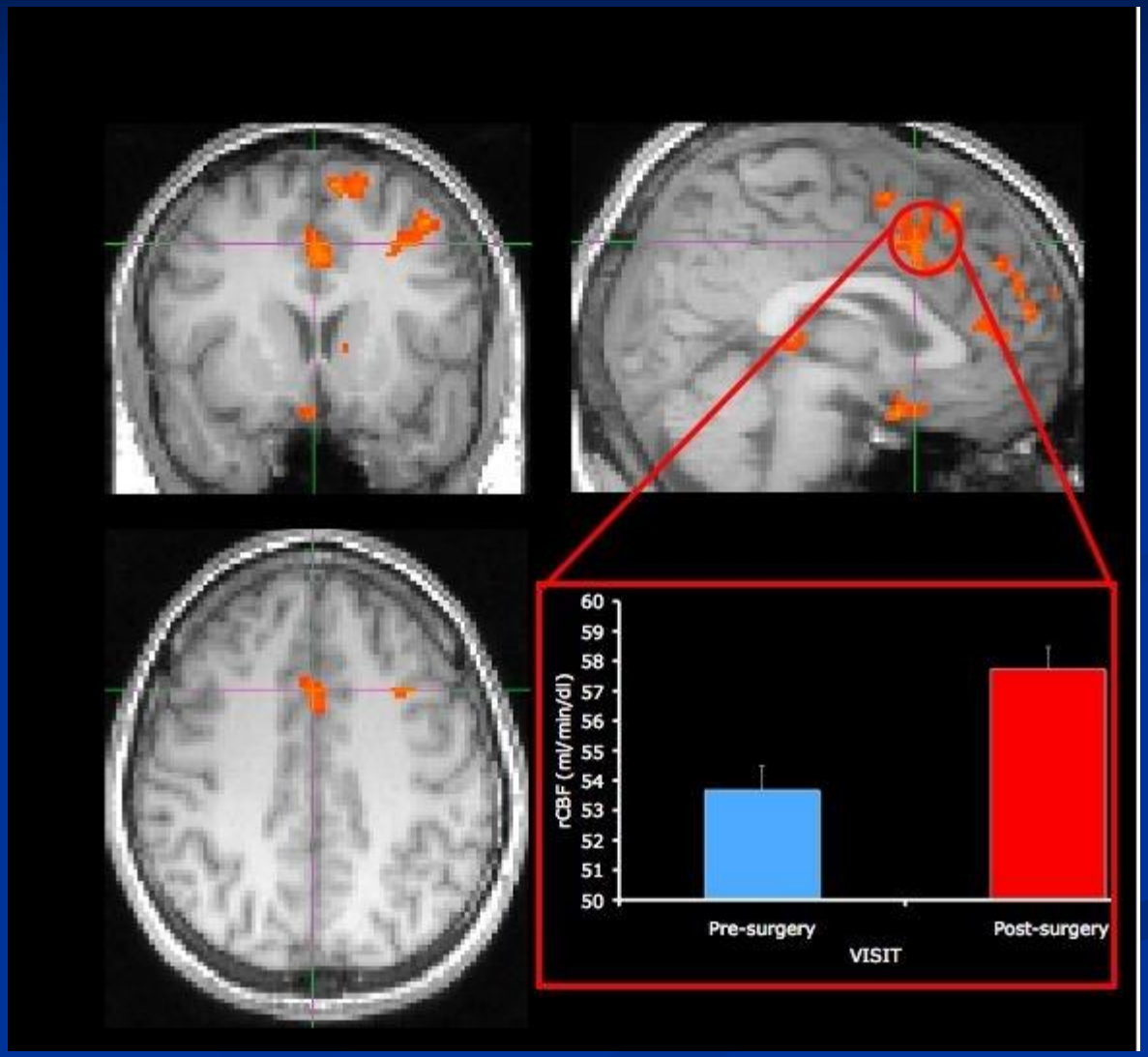




Assessment fMRI functional magnetic resonance imaging

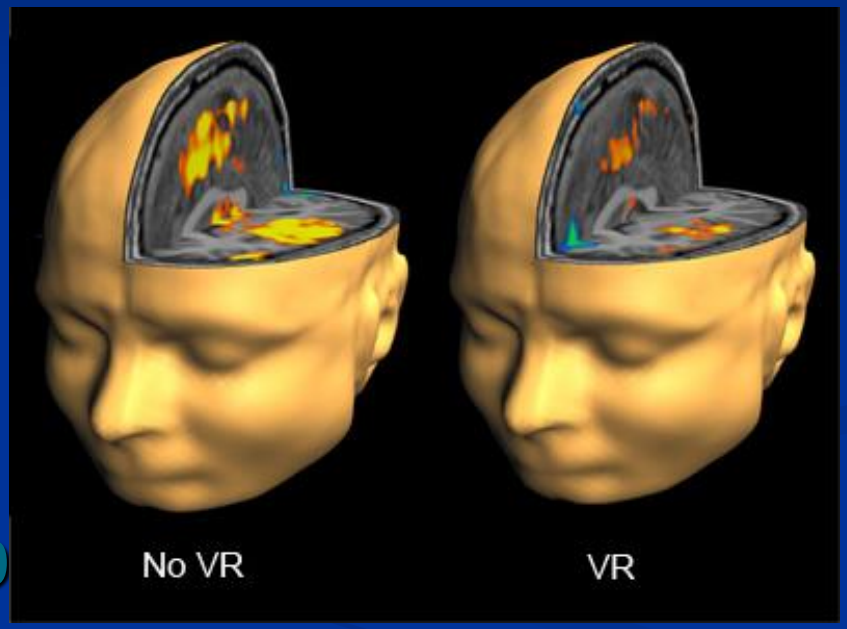






Management will depend on

- Inflammatory or neuropathic pain?
- Patient factors
- Environment

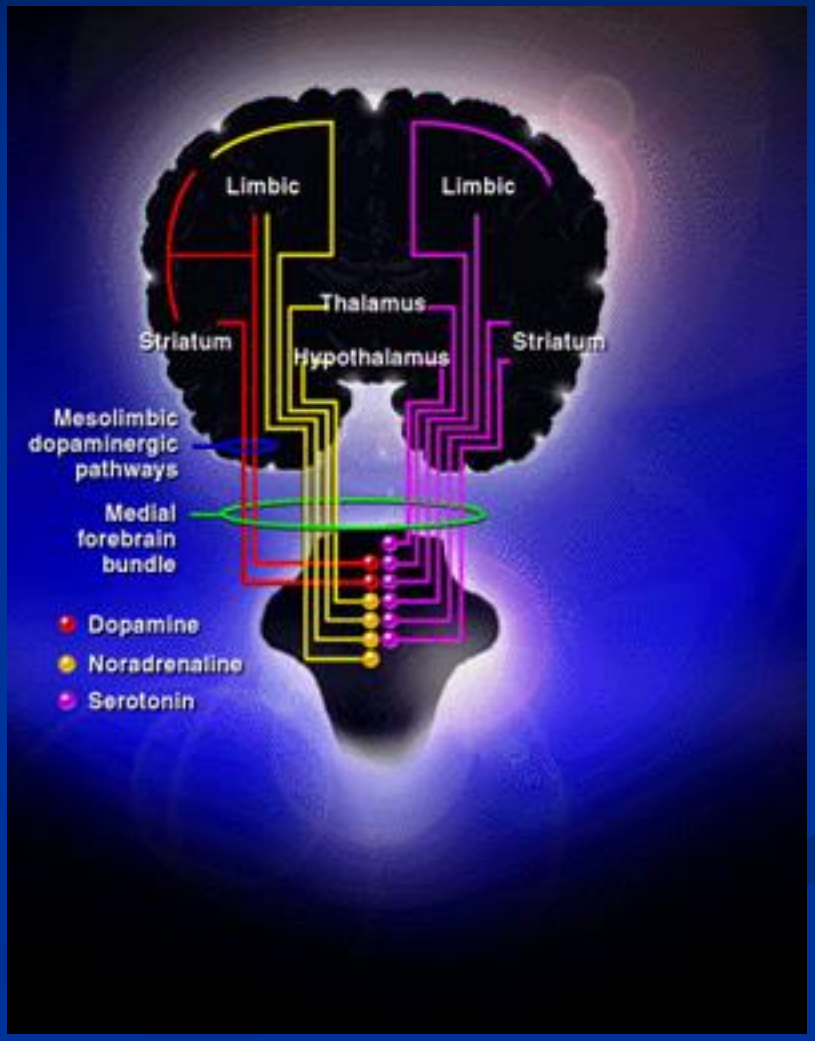


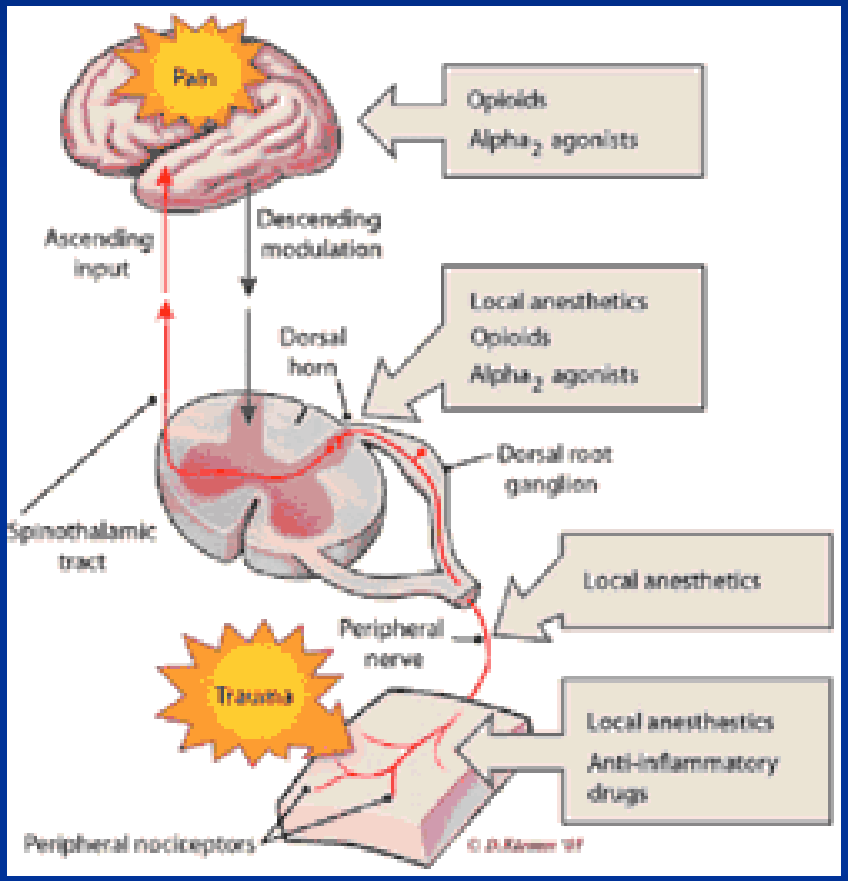
- **The future.....**
- Prevention of chronic p
- Earlier recognition
- Tailored individual treatment

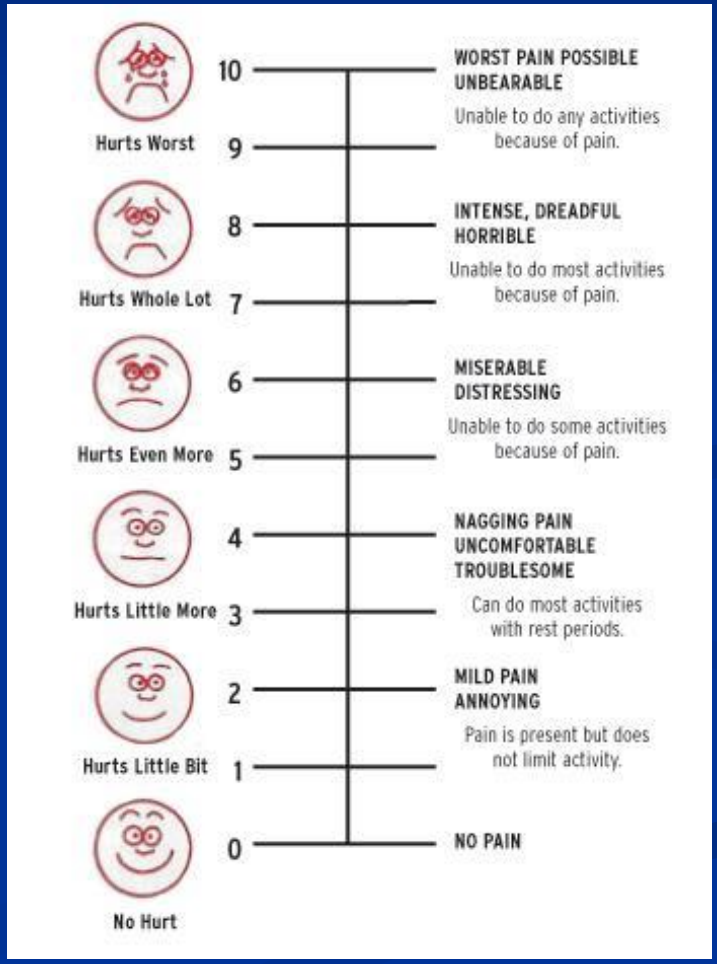
Thank you

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.

	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			

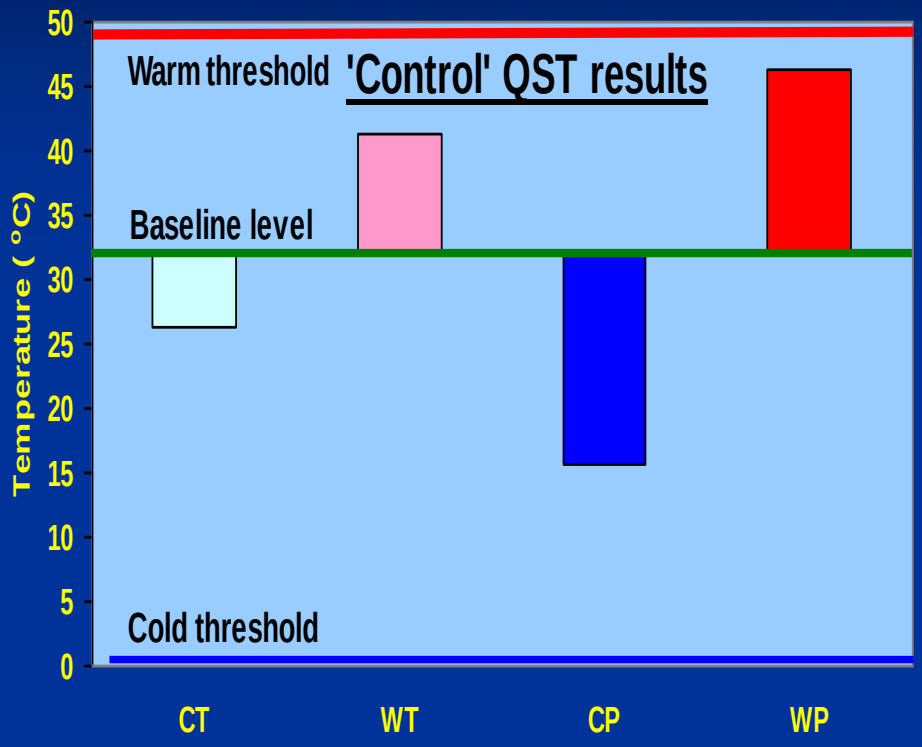
13	14	15	16
1 Fearful	1 Punishing	1 Wretched	1 Annoying
2 Frightful	2 Gruelling	2 Blinding	2 Troublesome
3 Terrifying	3 Cruel		3 Miserable
	4 Vicious		4 Intense
	5 Killing		5 Unbearable

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

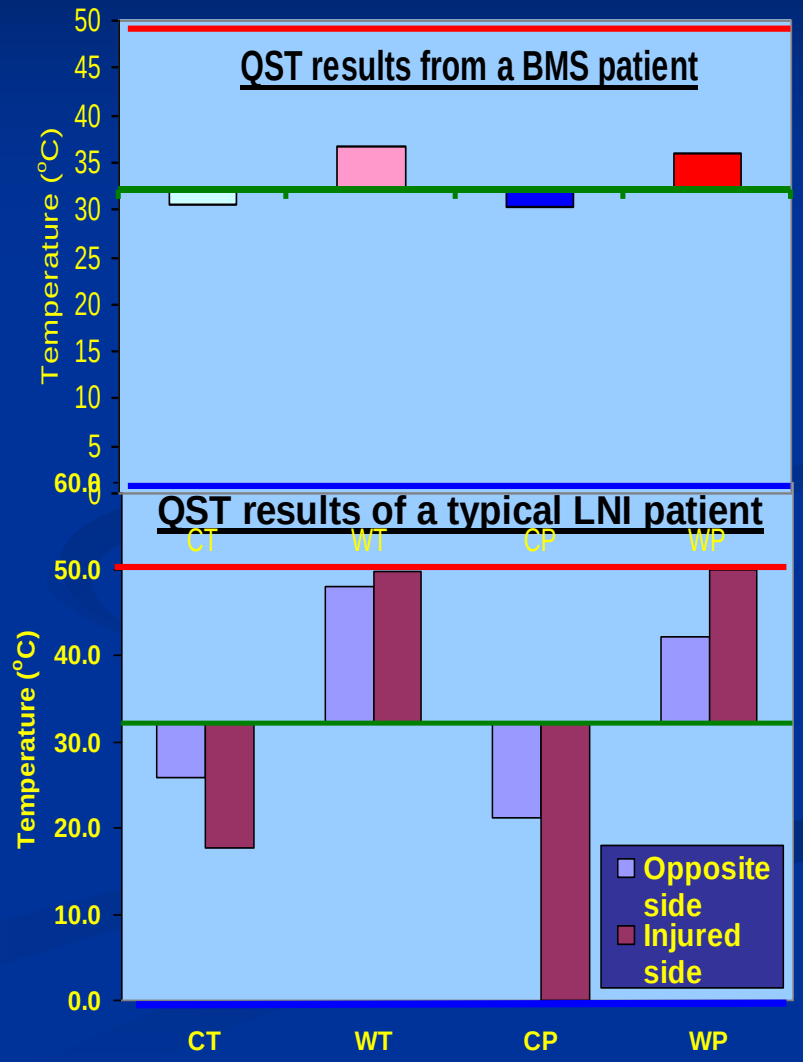
Sample thermal sensory results



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

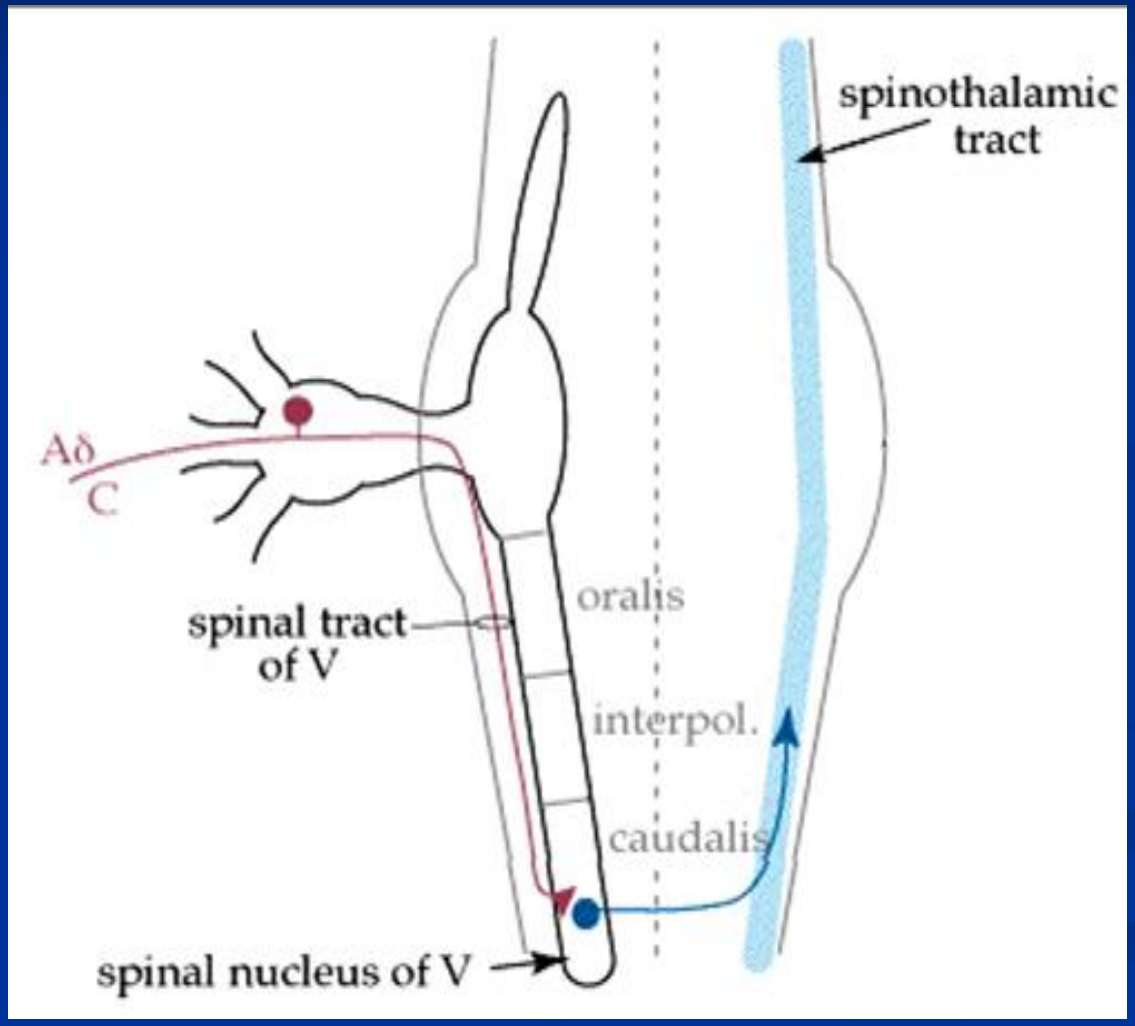
  29% high disability resulting in unemployment

  Von Korff et al 1992

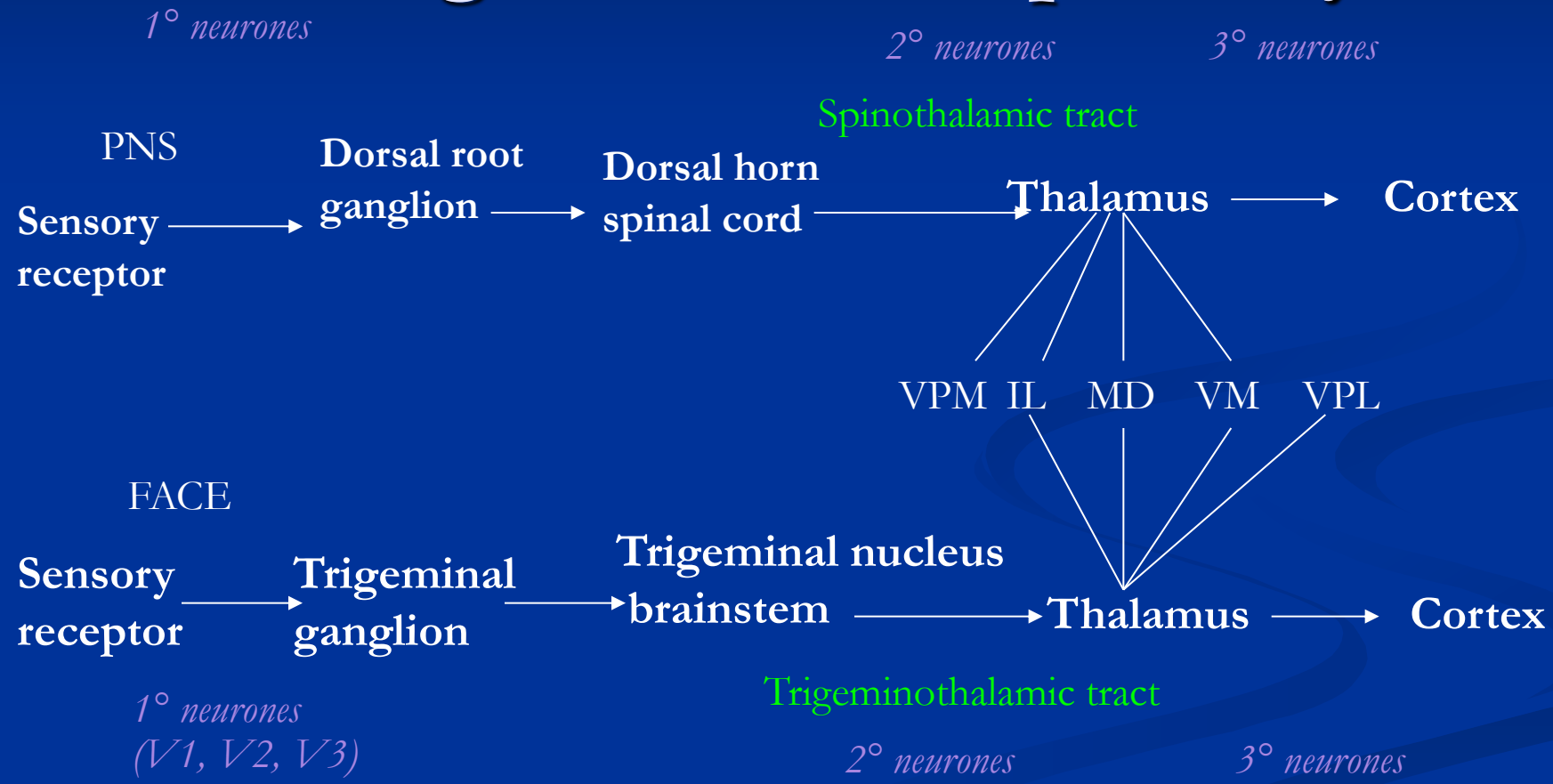
  64% decreased efficiency at work

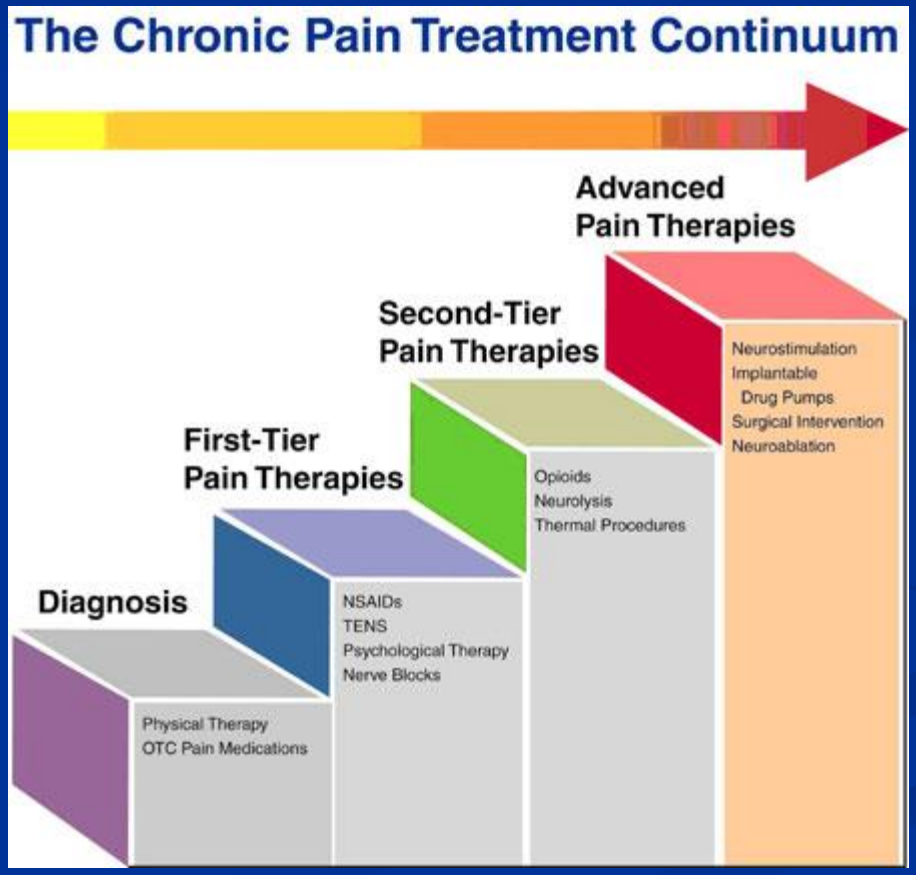
  Dao et al 1994

Pain/ temperature pathway



Somatosensory system
Trigeminal nerve pathway




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

Previous studies

Animal neurophysiological studies

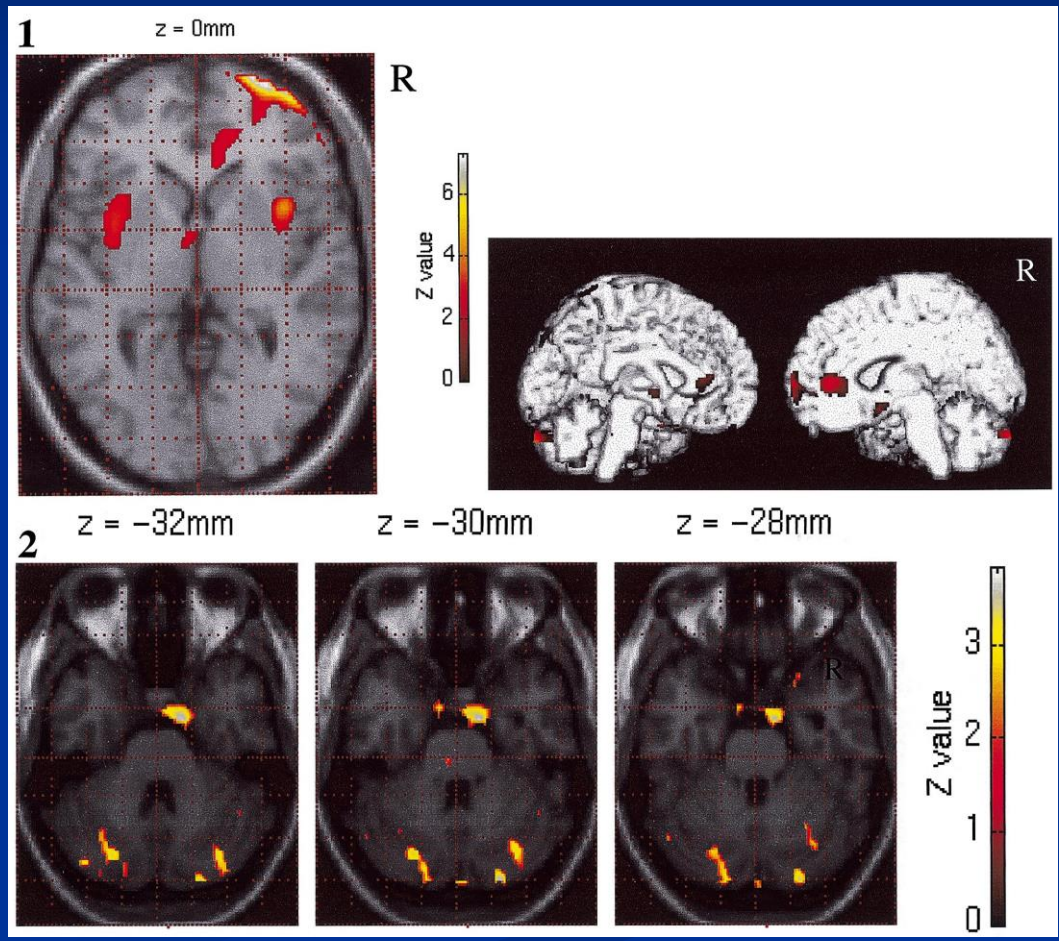
- Central neural changes following insult to the nervous system, leading to altered sensation, including pain.
- Data obtained from animal models not reflect CNS changes in humans.

PET & trigeminal system

- Fox et al. 1987- PET to localise functional areas of somatosensory cortex
- Weiller et al 1995- PET study- migraine without aura produced activation in brainstem (PAG) during the headache state cf headache free state
- May et 1998- capsaicin induced pain V1- activation insula cortex (IC) and anterior cingulate cortex (ACC) but not brainstem.
- More recent PET studies on cluster headaches-CNS disorder best considered as a form of neurovascular headache (May et al 2000)

PET limitations

- Non-invasive, but involves exposure to ionizing radiation- ethical for research?
- Lack of specificity
  - poor functional anatomy clarity for pain modelling
  - Inflammatory conditions
- Radioactivity decays rapidly so limited to monitoring short tasks



(Borsook et al 2004)

Functional MRI (fMRI)

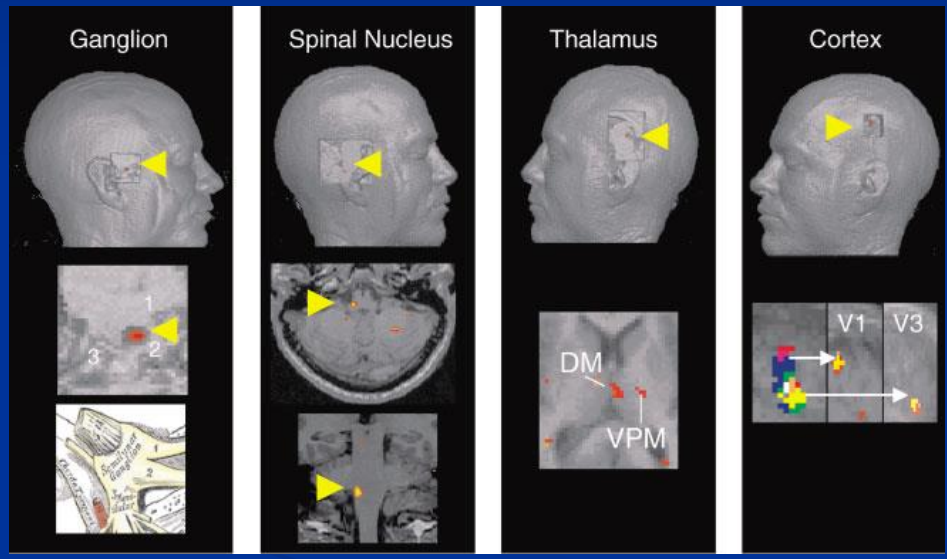
- **Pain** → neural activity → **haemodynamic response:**
  - Increased blood flow, increased blood oxygenation in active areas cf inactive areas.

- **Records brain activity** non-invasively by measuring:
  - Blood flow, Blood volume, Blood oxygenation

- Blood-oxygenation-level-dependent **(BOLD):**
  - Widely used in study of pain
  - detects differences in magnetic signal between oxyhg & deoxyhg
  - Identified pain matrix including: SI, IC, ACC, thalamus, PFC.

fMRI & trigeminal system to date

- Limited imaging studies of CNV
- Imaging CNV pathway to noxious heat stimulus to RHS face- activation ipsilateral TG & SpN, contralateral thalamus and cortex (Borsook et al 2003)
- Imaging activation in cortex to noxious heat stimulus to face and trigeminal nucleus- demonstrate & confirm somatotopy (DaSilva et al 2002)



(Borsook et al 2004)

Imaging trigeminal neuropathic pain

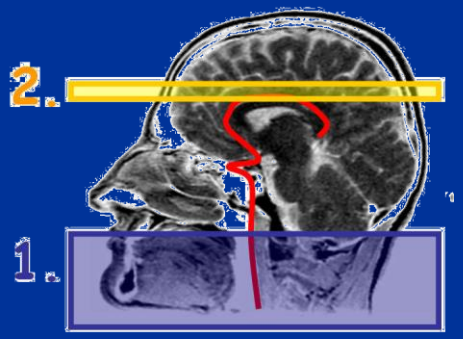
- Difficult diagnosis and lack of clinical/ radiographic abnormalities.
- ~22% adult population US experienced orofacial pain >once in previous 6/12 (Lipton et al. 1993).
- Limited studies of neuropathic pain in CNV system – recruitment difficulties
- PHN studies:
  - Flor et al 1995- CNS plasticity with sensory changes including pain in phantom limb patients
  - Geha et al. 2007- affective (ACC, IC & amygdale) & sensory discrimintive areas (thalamus, SI, SII) involved in spontaneous pain of PHN.
- Need further imaging studies to evaluate plasticity of cortical systems in TN.

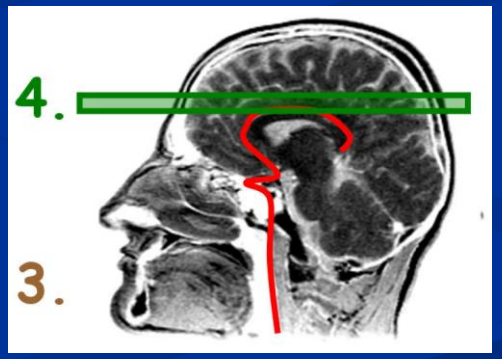
fMRI BOLD limitations

- Indirect measure of neural activity, susceptible to influence by non-neural changes in the body.
- Best suited to responses to changes in behaviour or stimulation.
- Not suitable for ongoing pain
- Can we overcome this with cASL?

Continuous Arterial Spin Labelling (cASL)

- Novel technique→ **quantitative** measure of cerebral blood perfusion throughout the brain in ongoing 'resting' states

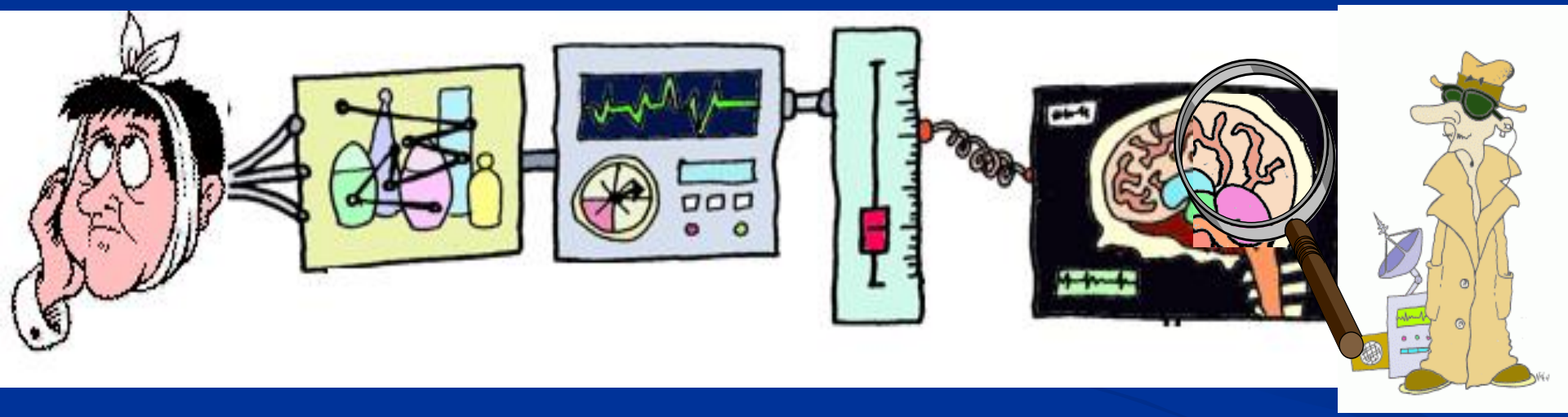




1. **Tag** inflowing arterial blood by magnetic inversion
2. Acquire the **tag image**
3. Repeat experiment without tag
4. Acquire the **control image**

Subtract: **Control image** magnetization - **Tag Image** magnetization **= rCBF**

The study

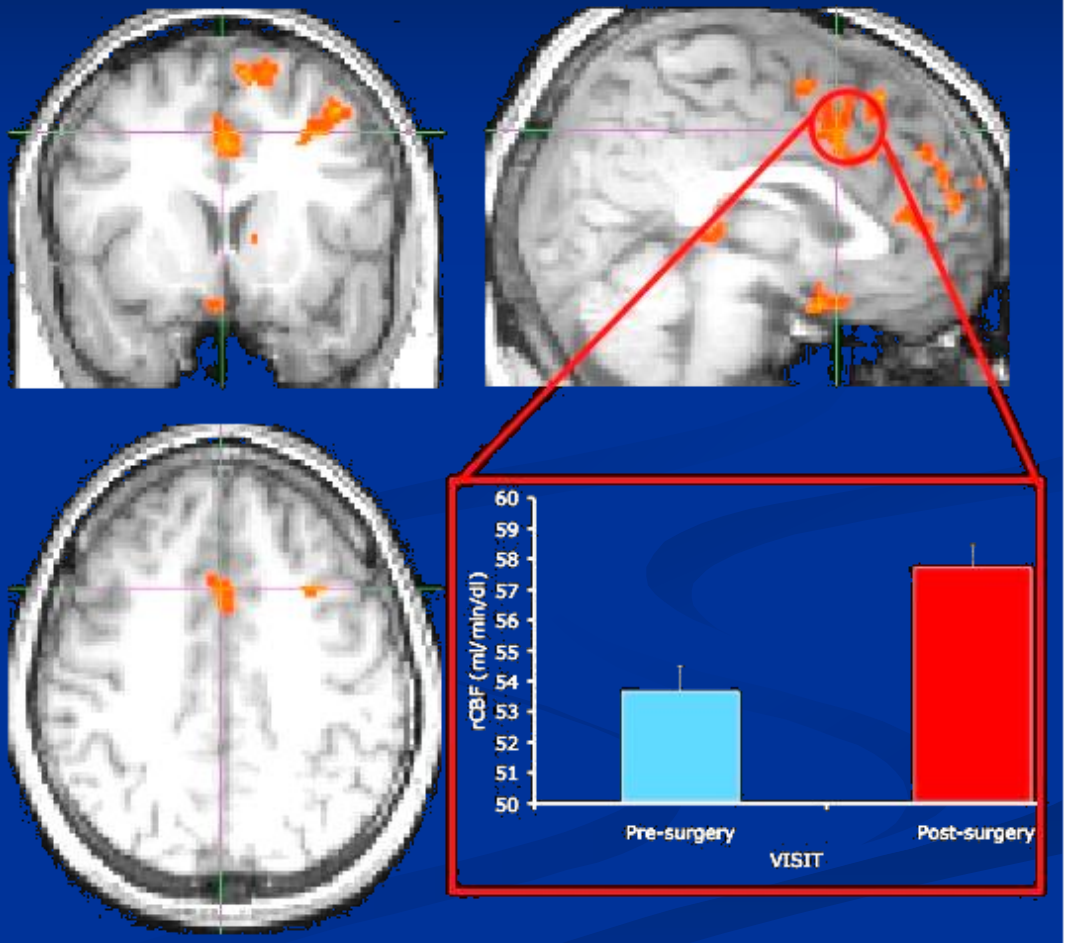


Objectives of study

- Third molar surgery (TMS) is the most frequently used acute post-surgical pain model in clinical trials of analgesia (Moore etal 2005).
- No likely systematic difference in analgesic efficacy TMS cf other post-surgical pain models (Barden et al. 2004).
- Aim to determine changes in rCBF in response to physiological perturbation of the trigeminal pain system following TMS, using cASL and assess any correlation of rCBF with patient's pain scores
- Establish Gold Standard Human objective analgesic model

A taster……

- Increase in rCBF in brain regions previously associated with pain including ACC, S1 and IC
- signal changes were significant, of the order of 5-10 %



Results applicable to;

- First application of methodology to acute pain- gold standard analgesic test model.
- Ultimately identify how analgesics work in CNS- development of this technique as a pain biomarker
- Trigeminal system vs PNS
- WATCH THIS SPACE!

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Pharmacological MRI (phMRI)

- fMRI used to evaluate the efficacy of drugs centrally
- Ultimately useful for testing efficacy of novel analgesics, especially in chronic pain
- Enable an objective, quantifiable measure of analgesic efficacy in addition to patients subjective measures.

Genetic diseases identified so far

- http://www.youtube.com/watch?v=1bQrQclRIrk