KING'S College LONDON

Orofacial pain: Diagnosis and management

- Tara Renton

Webinar: June 2011

An update

What is pain?

- Types of pain
- How do we feel it?

Orofacial pain

- Diagnosis
- Management

Cases

The Greek goddess of revenge ‘Poine’

- was sent to punish the mortal fools who had angered the gods.
- Poine also gave us our word "pain“
- Many ancient cultures believed pain and disease were punishment for human folly. "Magic and ritual were very common in ancient cultures”

- **‘Anaesthesia’**

  coined by Oliver Wendel Holmes, Sr. (1809–1894) in 1846 from the Greek αν-, *an-*, "without"; and αἴσθησις, *aisthēsis*, "sensation") refers to the inhibition of sensation

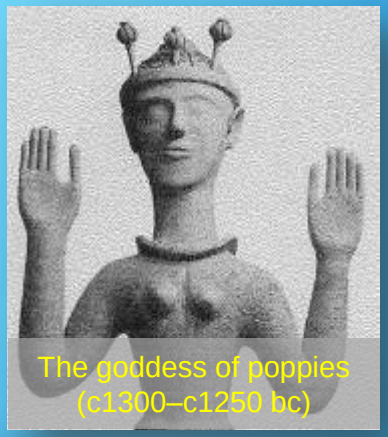
- **Analgesia**

  is the absence of pain

- **Pain**

  “An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (**IASP, 1979**).

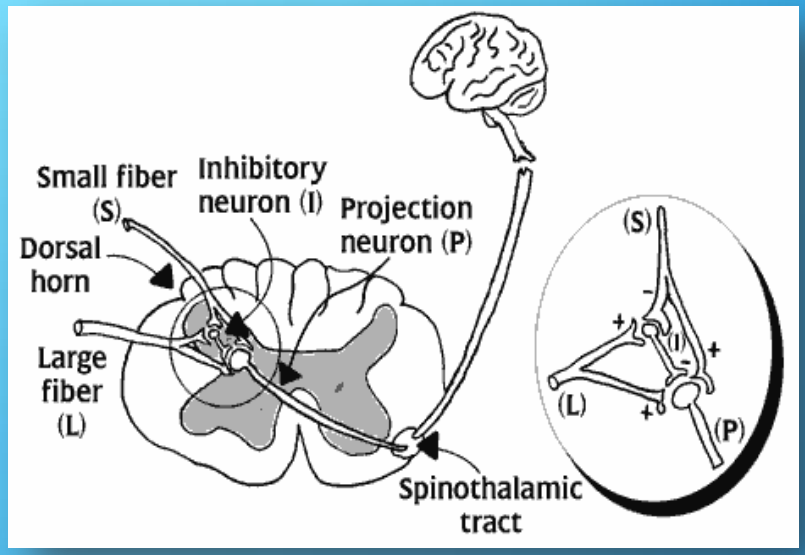
Understanding pain


The goddess of poppies (c1300–c1250 bc)

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

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

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



Gate Theory of pain

Canadian psychologist Ronald Melzak and British physiologist Patrick Wall (1965)

Celsus (25 BC) remarks that toothache *"can be counted among the greatest of torments"*

"For there was never yet philosopher that could endure the toothache patiently."

Shakespeare, *Much Ado About Nothing*, Act V

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	
Measure	• questionnaires to assess disability • physical / mental

HOW DO WE FEEL THE "OUCH“?

Pain Process

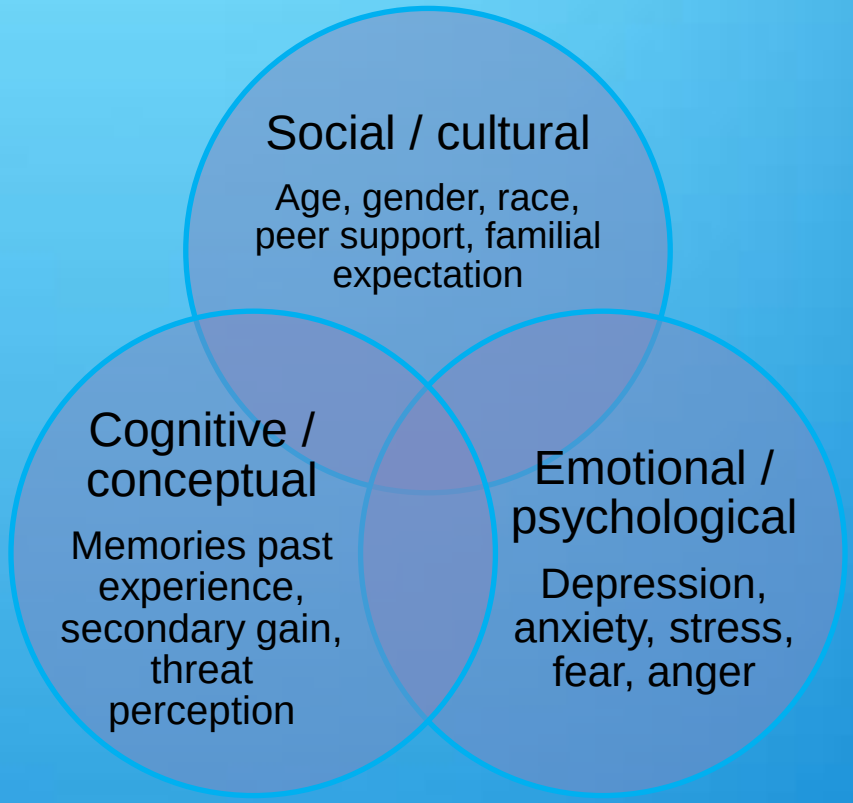
Nociception

Sensation

Behaviour

Suffering

Bio psycho social Model



NEURAL PROPAGATION OF PAIN

Nociception

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

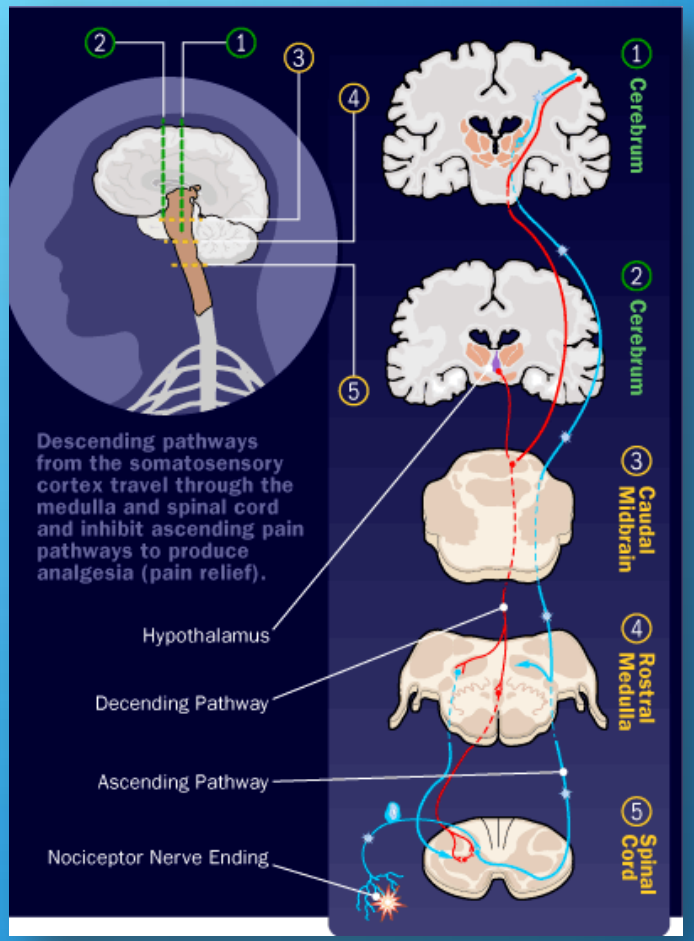
Noxious stimulus
What events unfold in the **sensory** system?

Neurophysiological

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

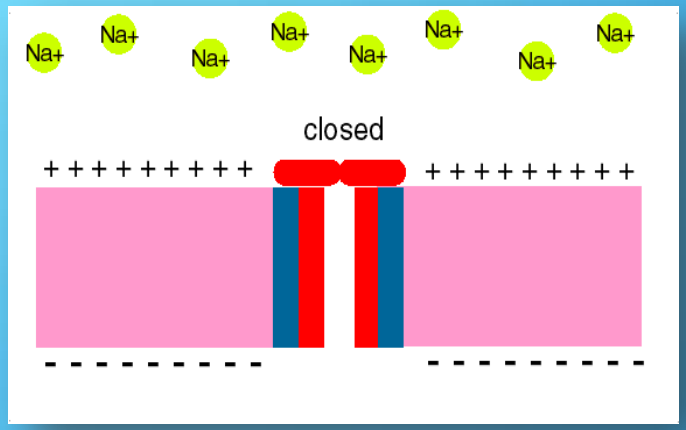
Patient

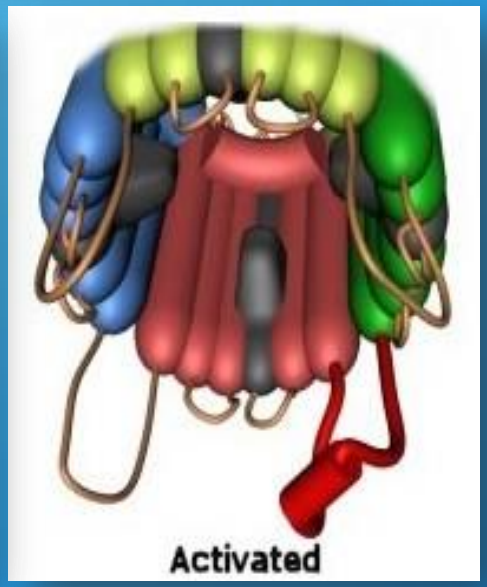
- Clinical symptoms
- Psychological factors
- Environmental factors
- **Reaction is Emotional and Physical**



Specific pain receptors

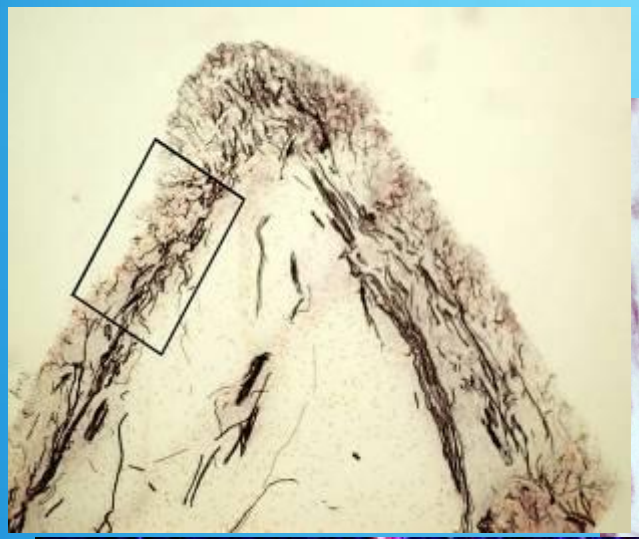
- Transmitters
  ↓NGF, ↓ SP, ↓ CGRP
- Receptors
  ↓ TRPV1, ↓ P2X3
- Ion Channels
  - Na, Ca, K
- Anatomy
  - degeneration
- ↑ spontaneous activity

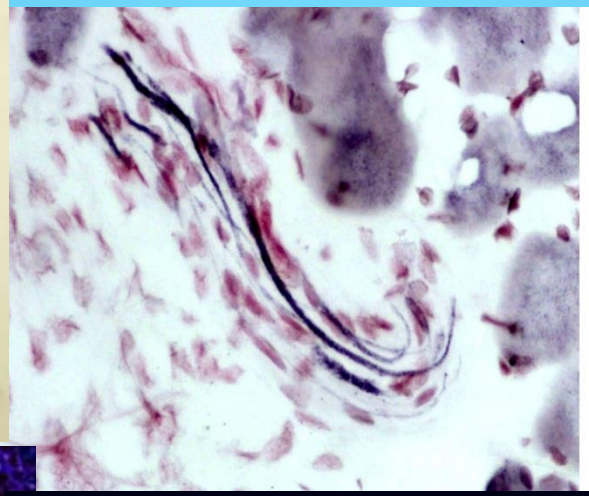


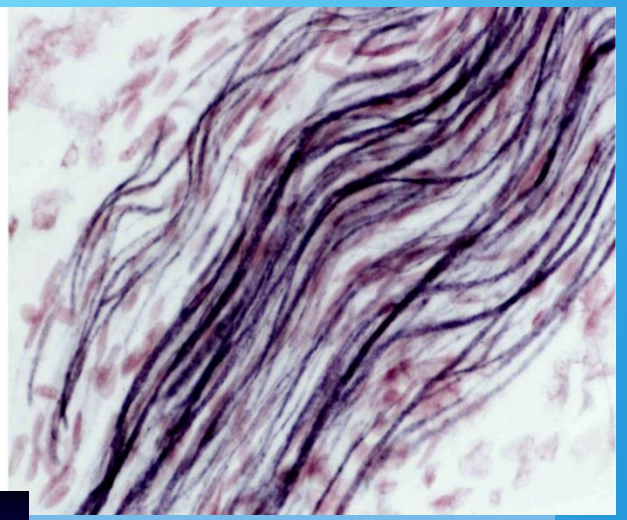


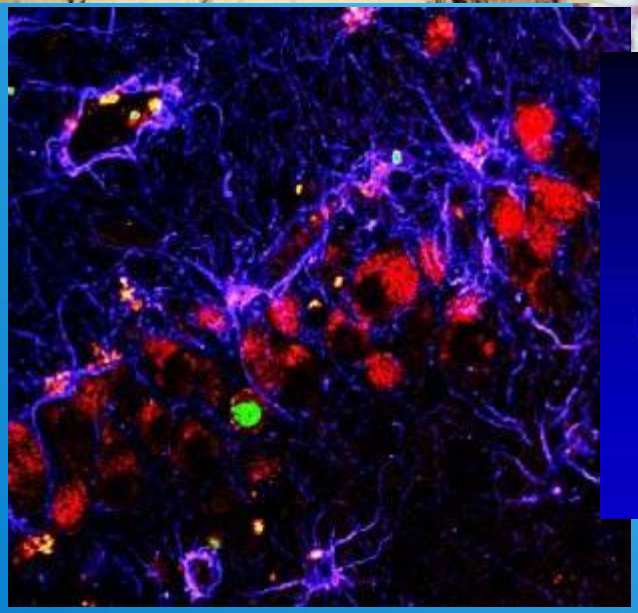
Control

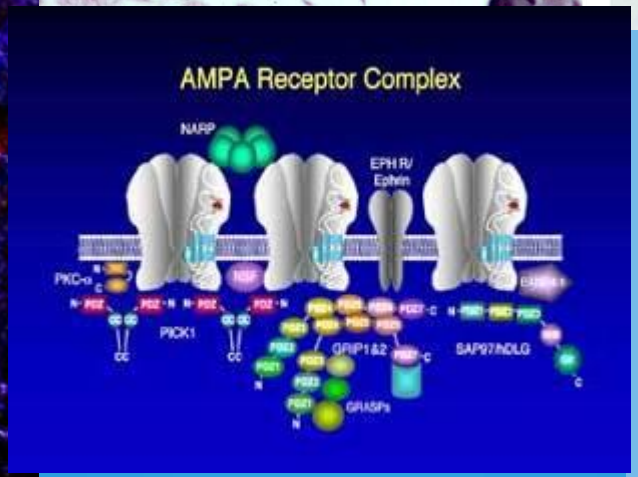
Pain

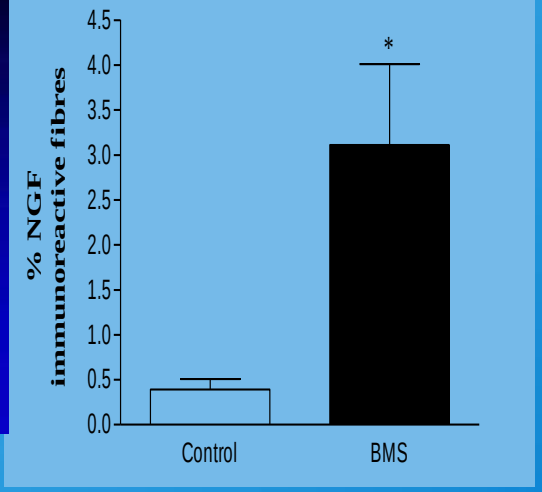






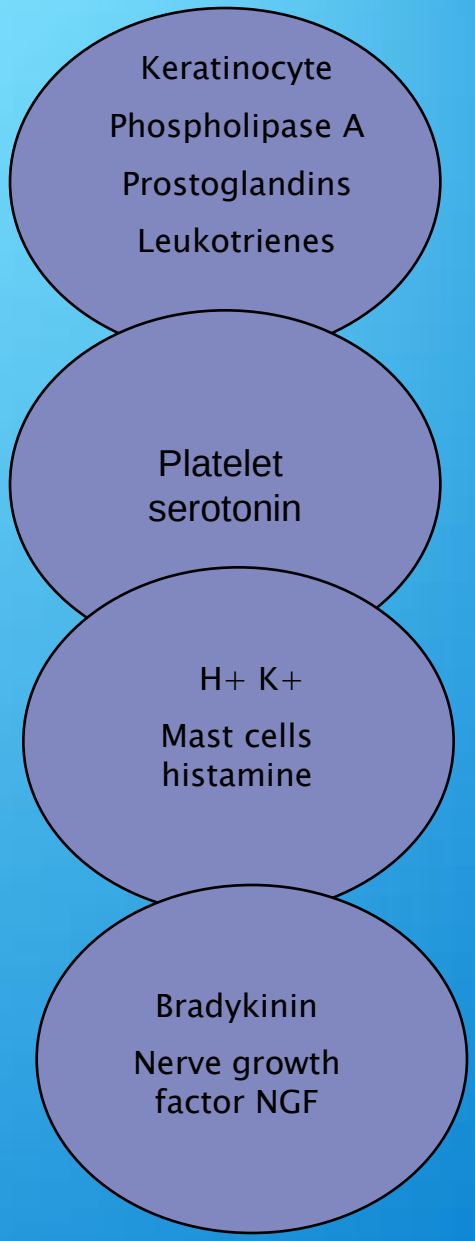






Peripheral Acute inflammatory pain

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



CNS and PNS

Receptor

Primary sensory nerve

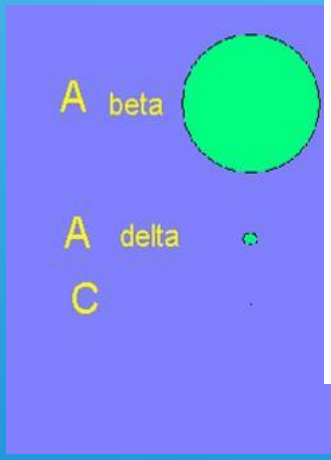
- A Delta and C fibres

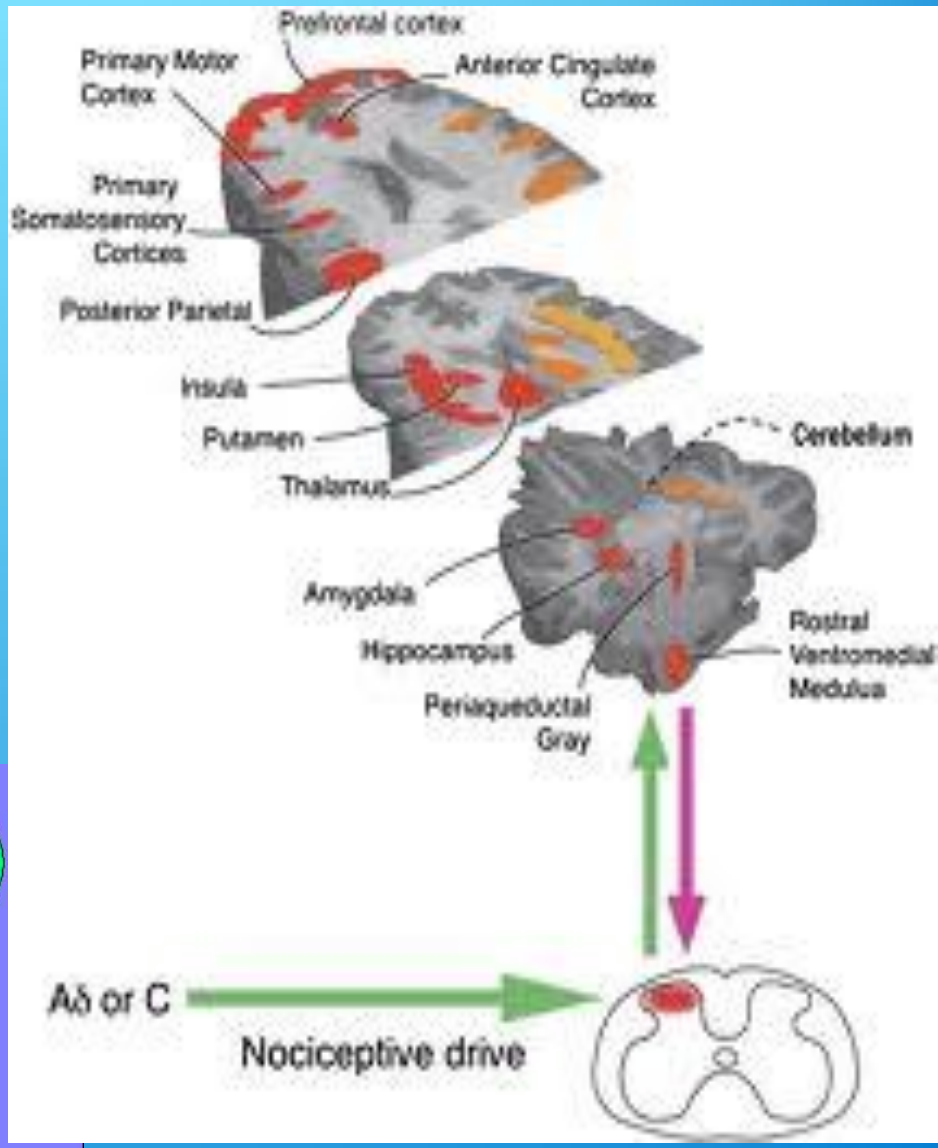
Secondary sensory nerve

- Lamina I DRG

Tertiary sensory nerve

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

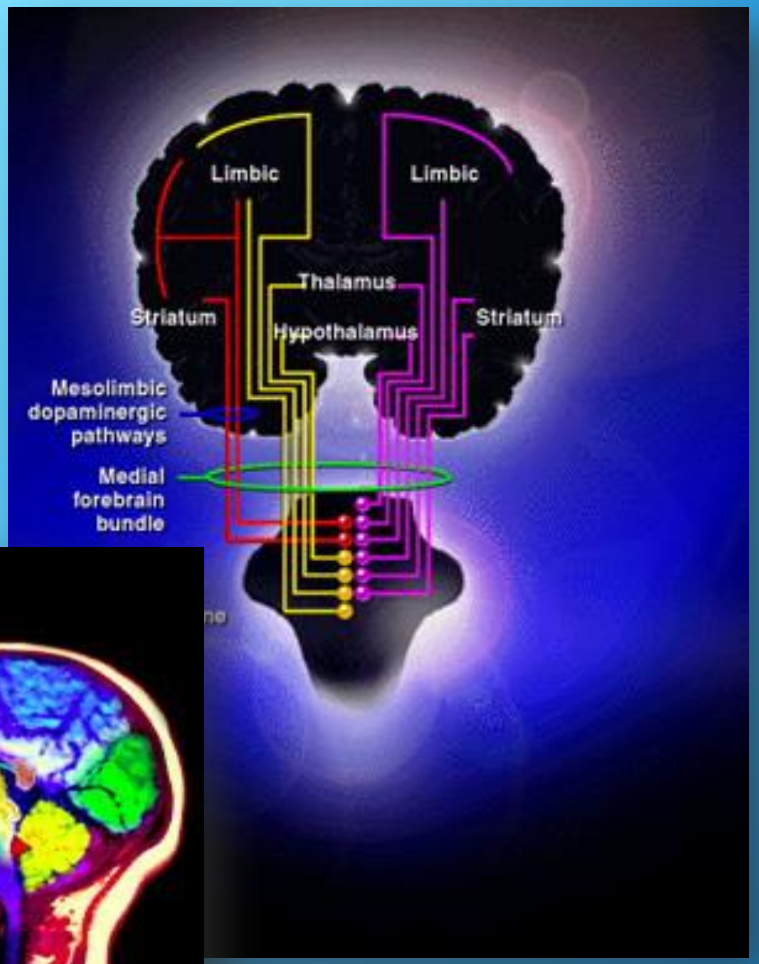


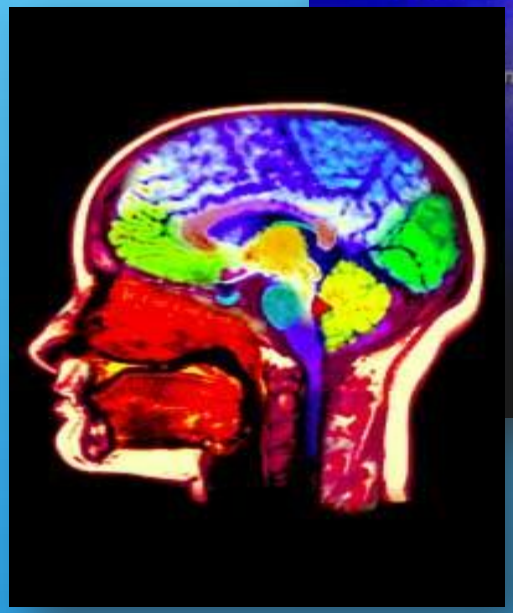


SENSATION

Central neuroanatomy

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





Anatomy revisited

ACC

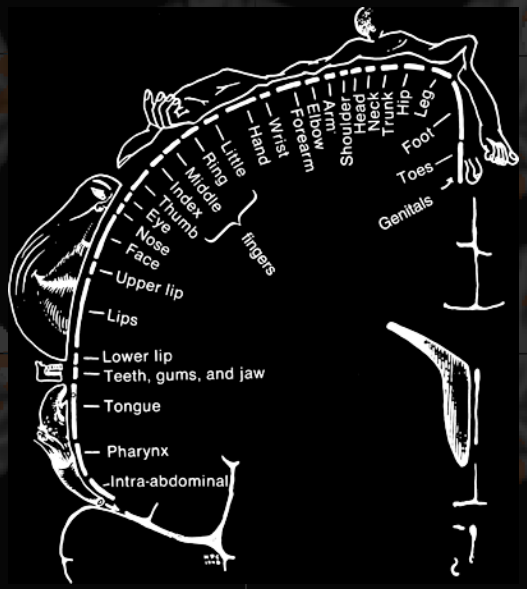
PCC

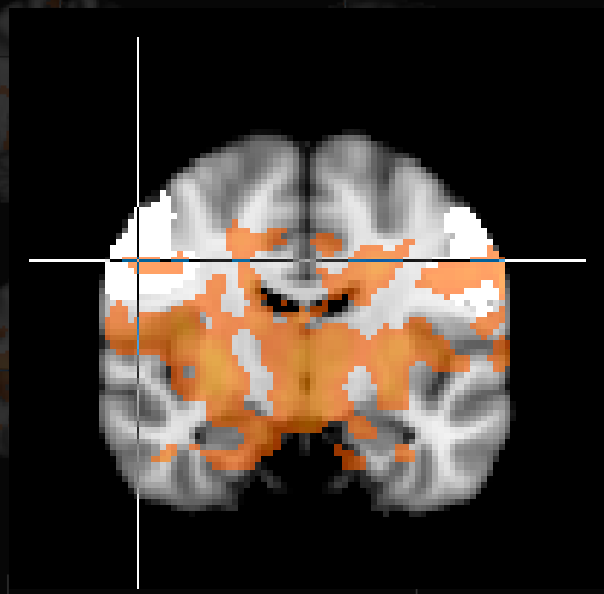
S1

S2

THAL

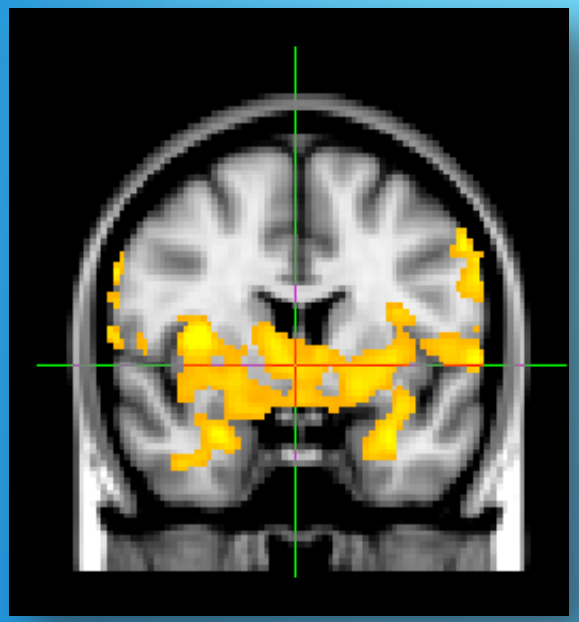
INS

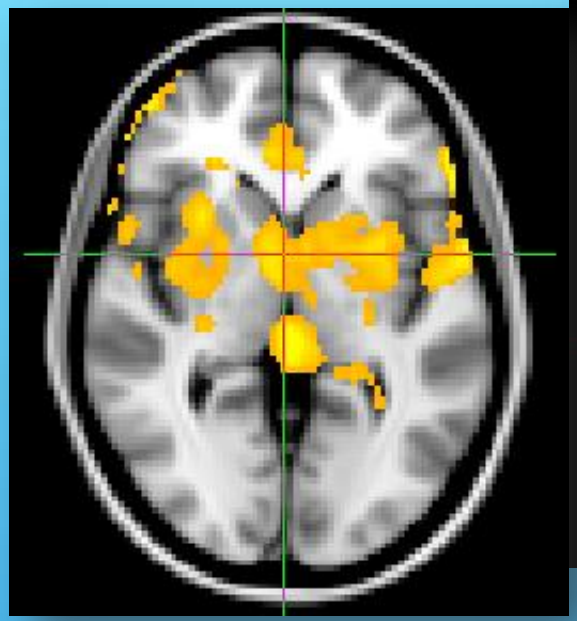


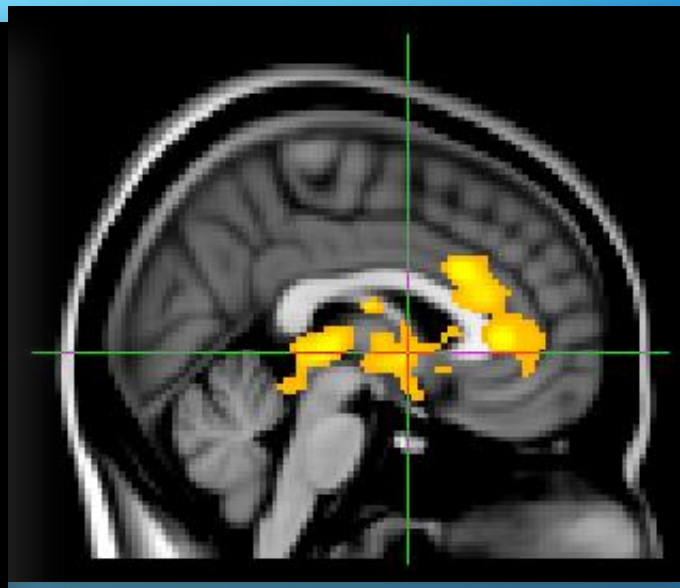


•Additional amygdala, hippocampus, brainstem, and V5 ROIs

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
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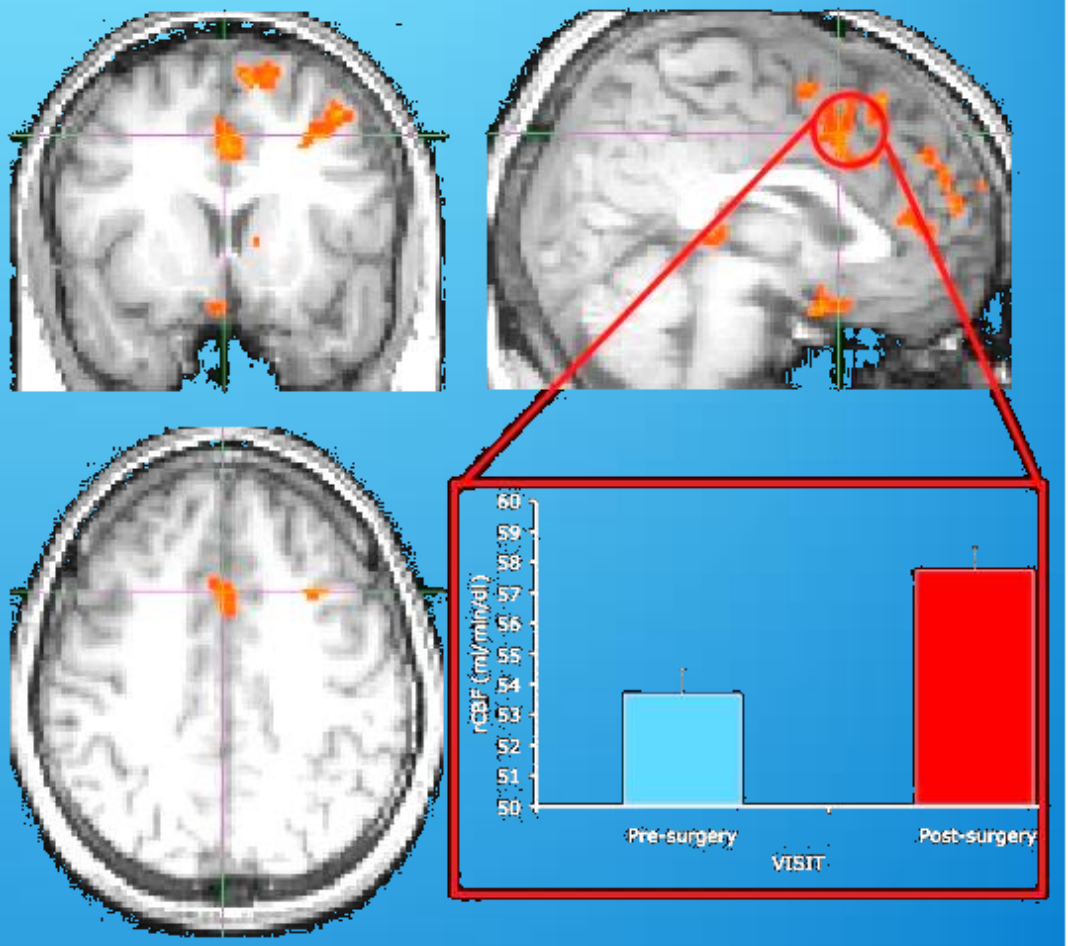
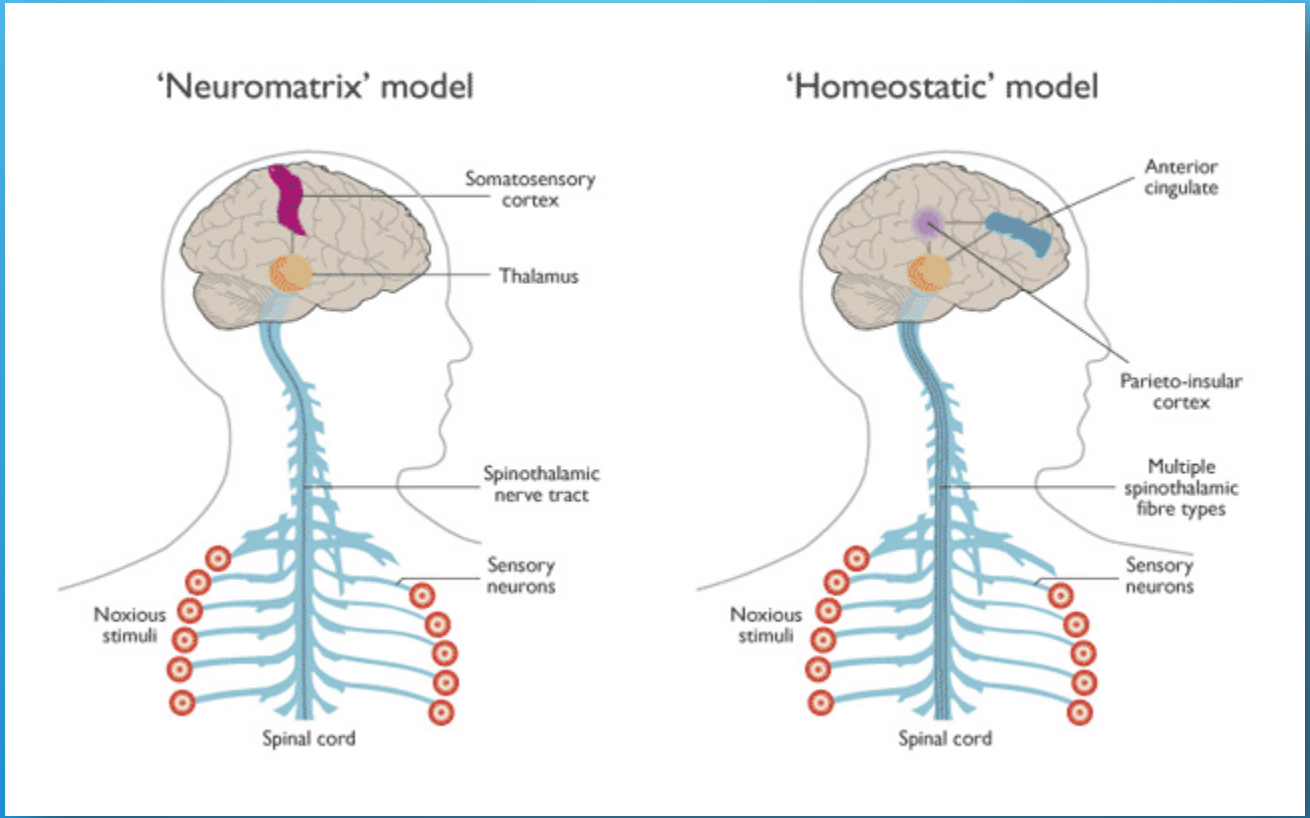


Behaviour

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

Affective emotional areas of Brain

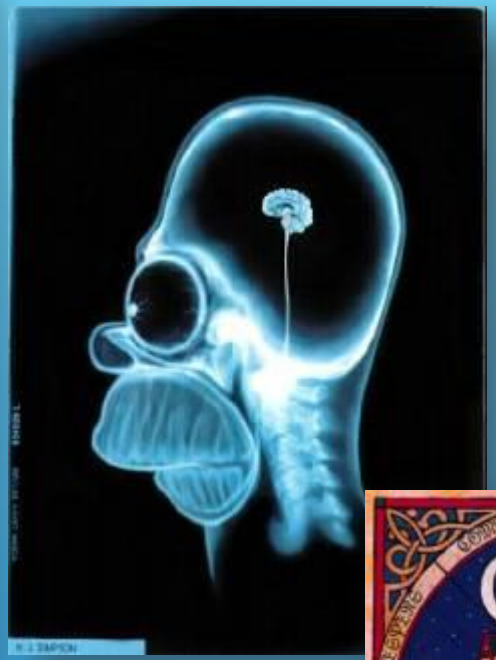


Perception of pain

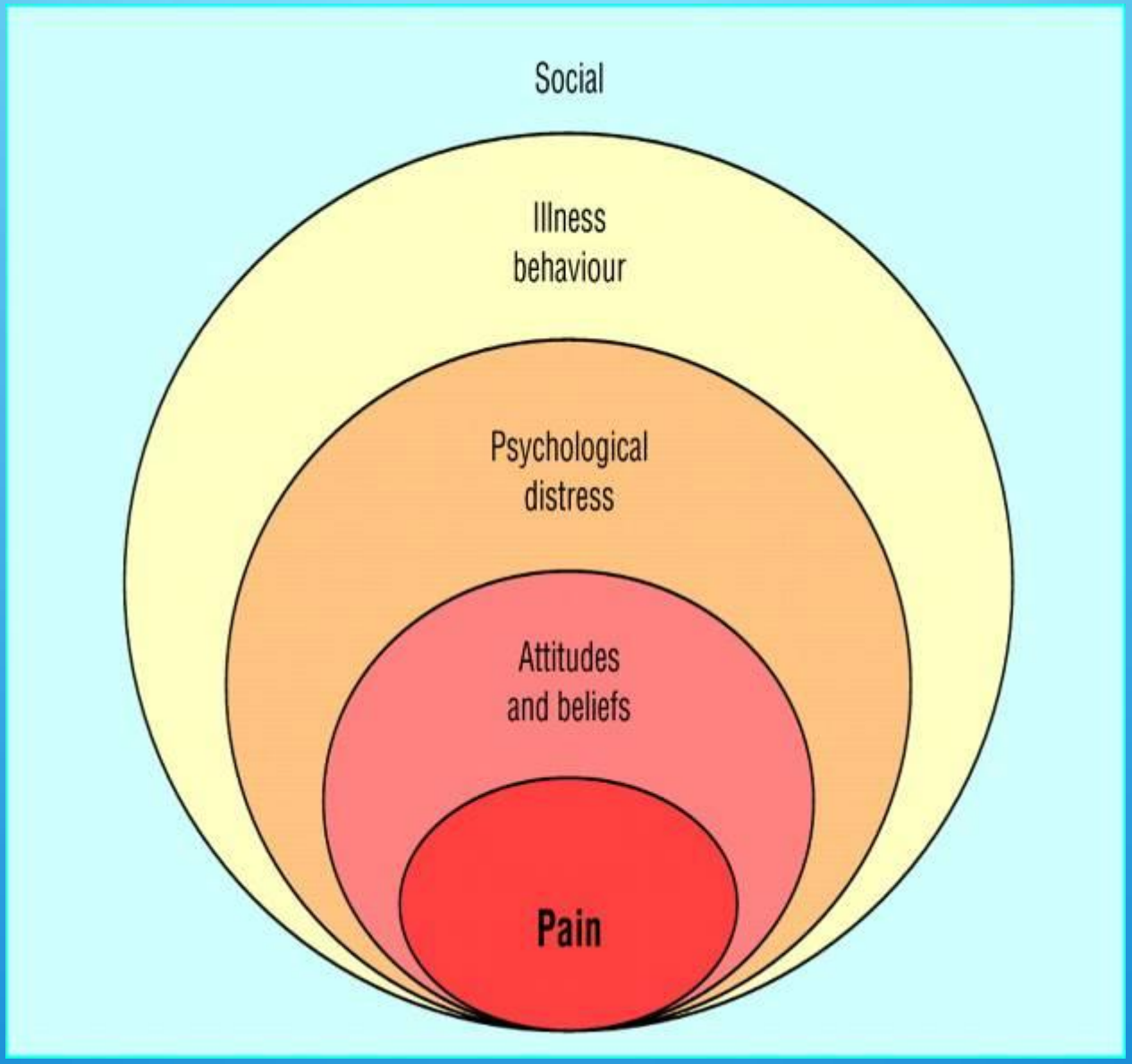
Perception of pain

‘I enjoy the pain’

David Beckham on tattoos



Opus Dei Priest ‘Pain is good’

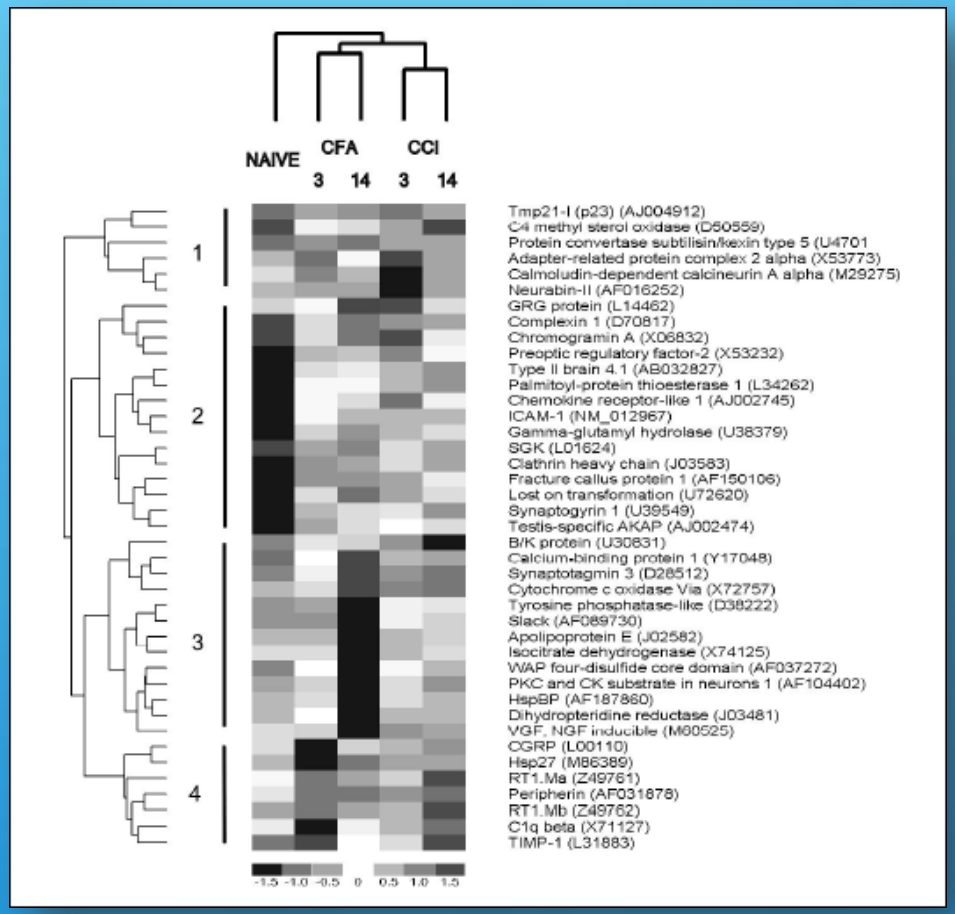

Social
Illness behaviour
Psychological distress
Attitudes and beliefs
Pain

Suffering

History
Stress
Anxiety
Culture
Ethnicity
Beliefs
Age
Environment
Context

Personality
Religion
Placebo
Anger
Catastrophising
Fear

Genetics and pain



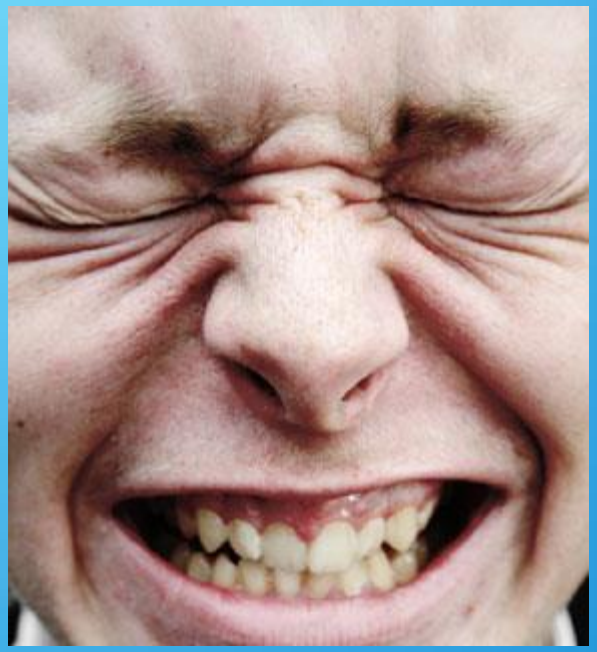
The Human Genome

- 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

COMT(catechol-O-methyl transferase)

- The COMT protein is a brain janitor and metabolizes the brain chemicals called dopamine and norepinephrine.
- Dopamine is often known as the brain's "**pleasure chemical**", because of its role in transmitting signals related to pleasurable experiences.
- If you have:
  - two copies of the **val** form of COMT that mops up dopamine rapidly
  - two copies of the **met** form of the gene make only poor COMT, and can't "clean up"
  - one copy of each gene variety -- the majority of people -- make some of each kind of COMT, yielding a "normal" dopamine-metabolizing system.
- The differences between met/met and val/val participants in the activation of the mu-opioid system were most significant in the cingulate cortex, thalamus and the **nucleus accumbens**

Genetics of pain

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

Candidate genes so far

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

The future of pain genetics

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

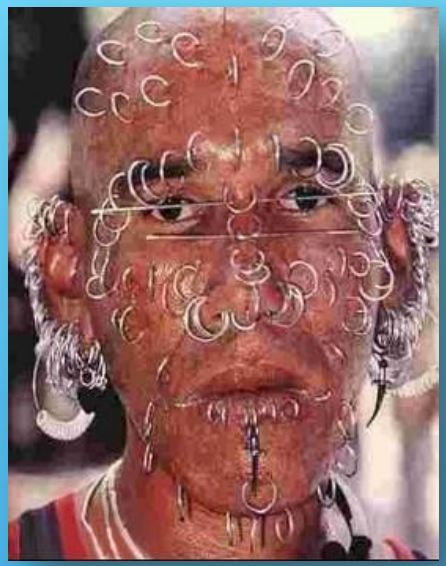
TYPES OF PAIN

Pain: Acute

‘Healthy pain’ due to inflammation

Infection / autoimmune / trauma

Thermal / mechanical / chemica



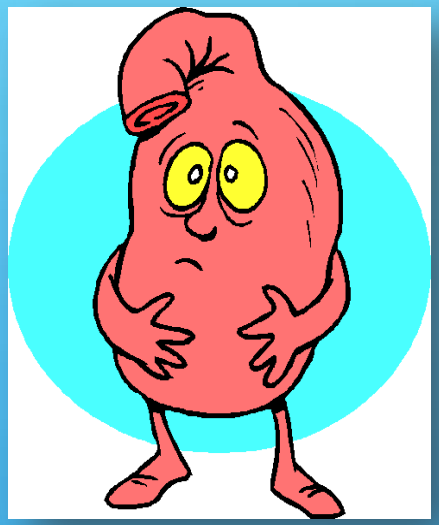
Chronic Pain

Unhealthy / Neuropathic pain lasting > 3 months

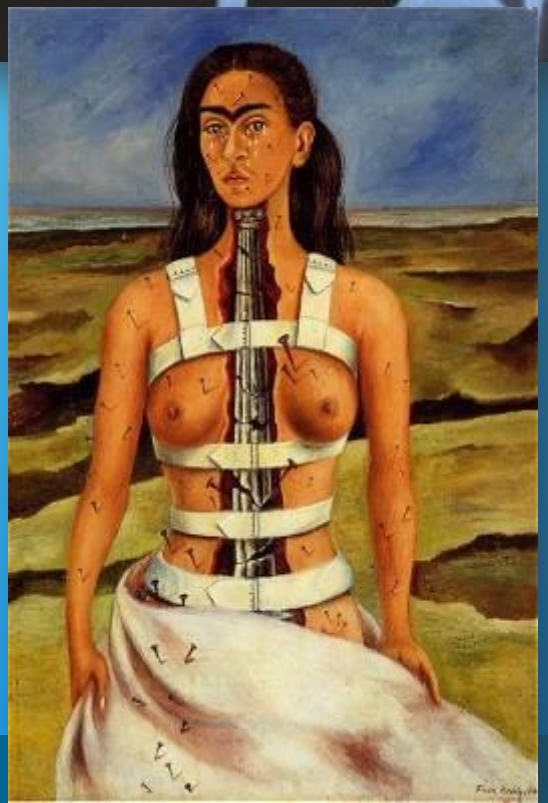
Back pain 47.5%

Head ache 45.2%

Joints 41.7%



Disease of the neuromatrix



Chronic pain: consequences UK

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

Consequences of pain: US

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.

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 pain

Education

Complex region

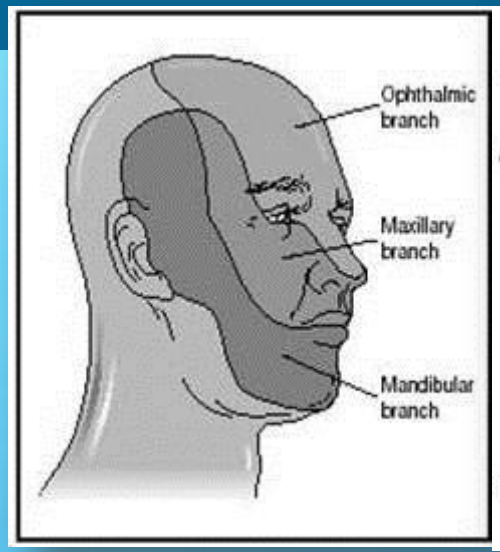
Consequences

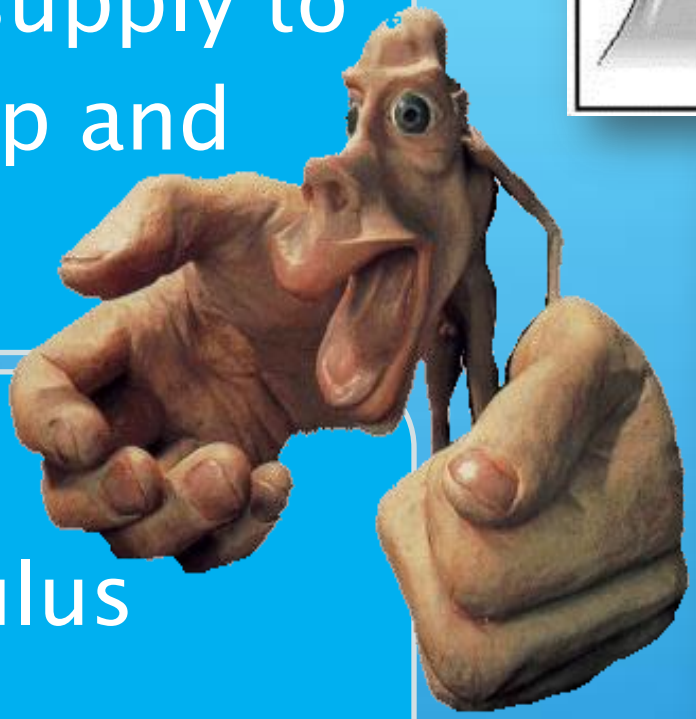
- Social function
- Eating
- Drinking
- Speaking
- Kissing
- Make up / shaving
- Sleeping

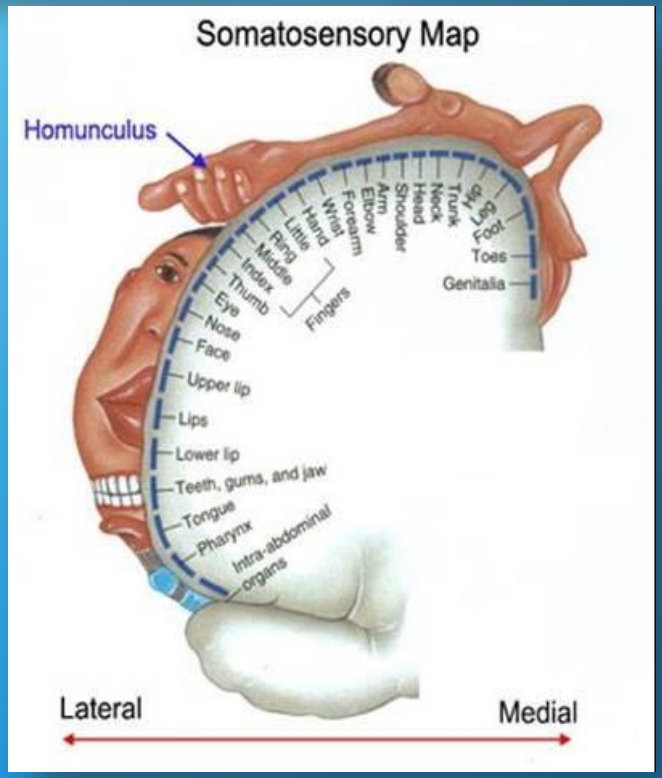
Trigeminal nerve

Sensory supply to face, scalp and mouth

Homunculus







Causes of peripheral sensory nerve neuropathy

- Diabetes
- HIV
- PHN
- Chemotherapy
- MS
- Post surgical traumatic neuropathy
- Parkinson's
- Malignancy
- Drugs – Growth hormone injections

Kehlet *et al*, 2006 in Lancet

	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	US surgical volumes (1000s)†
Amputation[2]	30–50%	5–10%	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy)[3]	20–30%	5–10%	479
Thoracotomy[4–7]	30–40%	10%	Unknown
Inguinal hernia repair[8–10]	10%	2–4%	609
Coronary artery bypass surgery[11–13]	30–50%	5–10%	598
Caesarean section[14]	10%	4%	220

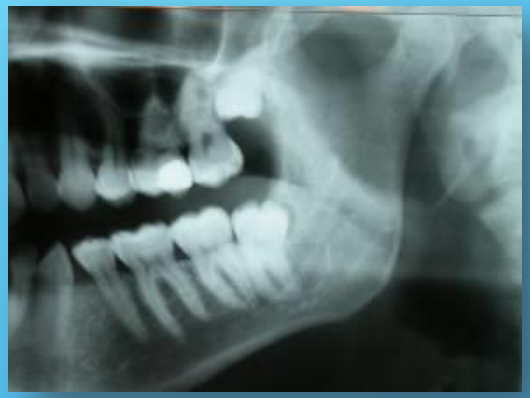
*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

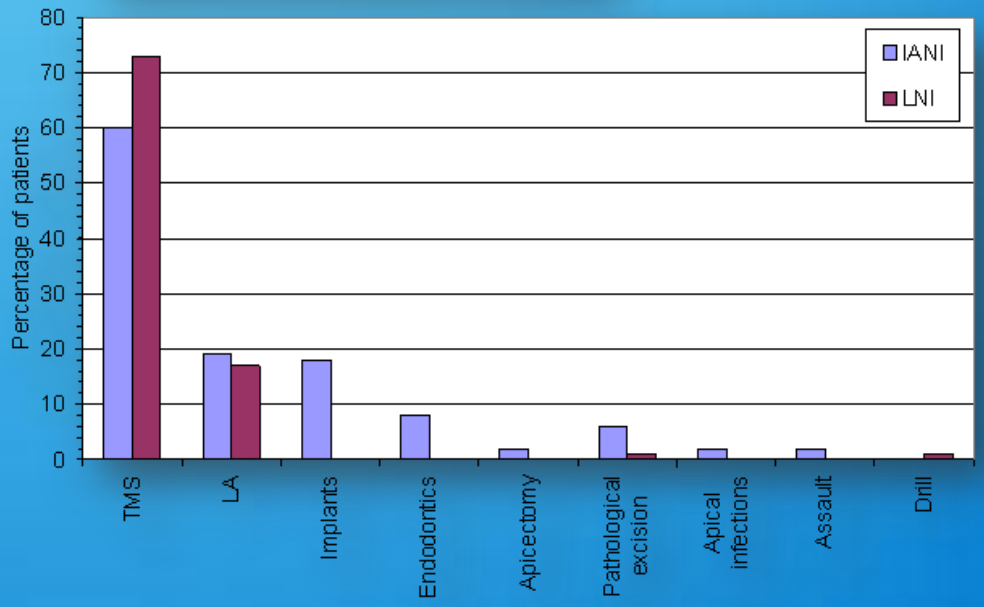
Table 1: **Estimated incidence of chronic postoperative pain and disability after selected surgical procedures***

30% get persistent pain10% are severely affected
? 4–5% of trigeminal severely affected

Post traumatic neuropathy of the trigeminal nerve

- Local anaesthesia
- Third molar surgery
- Implants
- Endodontics
- Orthodontics
- Orthognathic surgery
- Fractures
- Pathology





THE CONSEQUENCES OF TRIGEMINAL NERVE INJURY

Impact of orofacial pain

70% psychological impact

Locker & Grushka 1987

48% psychosocial impact

Richards & Slade 1996

In TMJ pain:

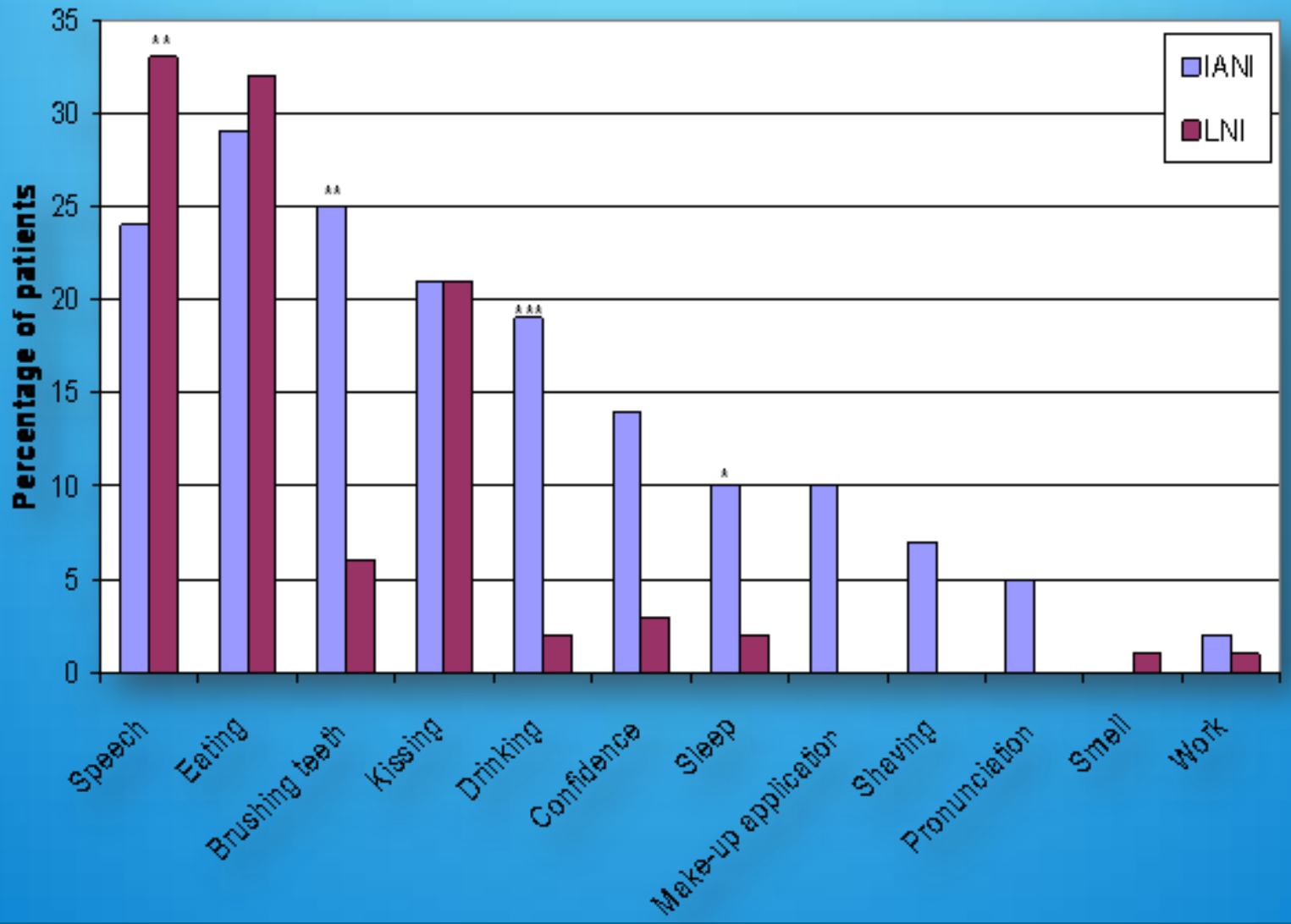
- 29% high disability resulting in unemployment

  Von Korff et al 1992

- 64% decreased efficiency at work

  Dao et al 1994

Interference of symptoms with the lifestyle for IANI and LNI patients.



Classification of Chronic orofacial pain

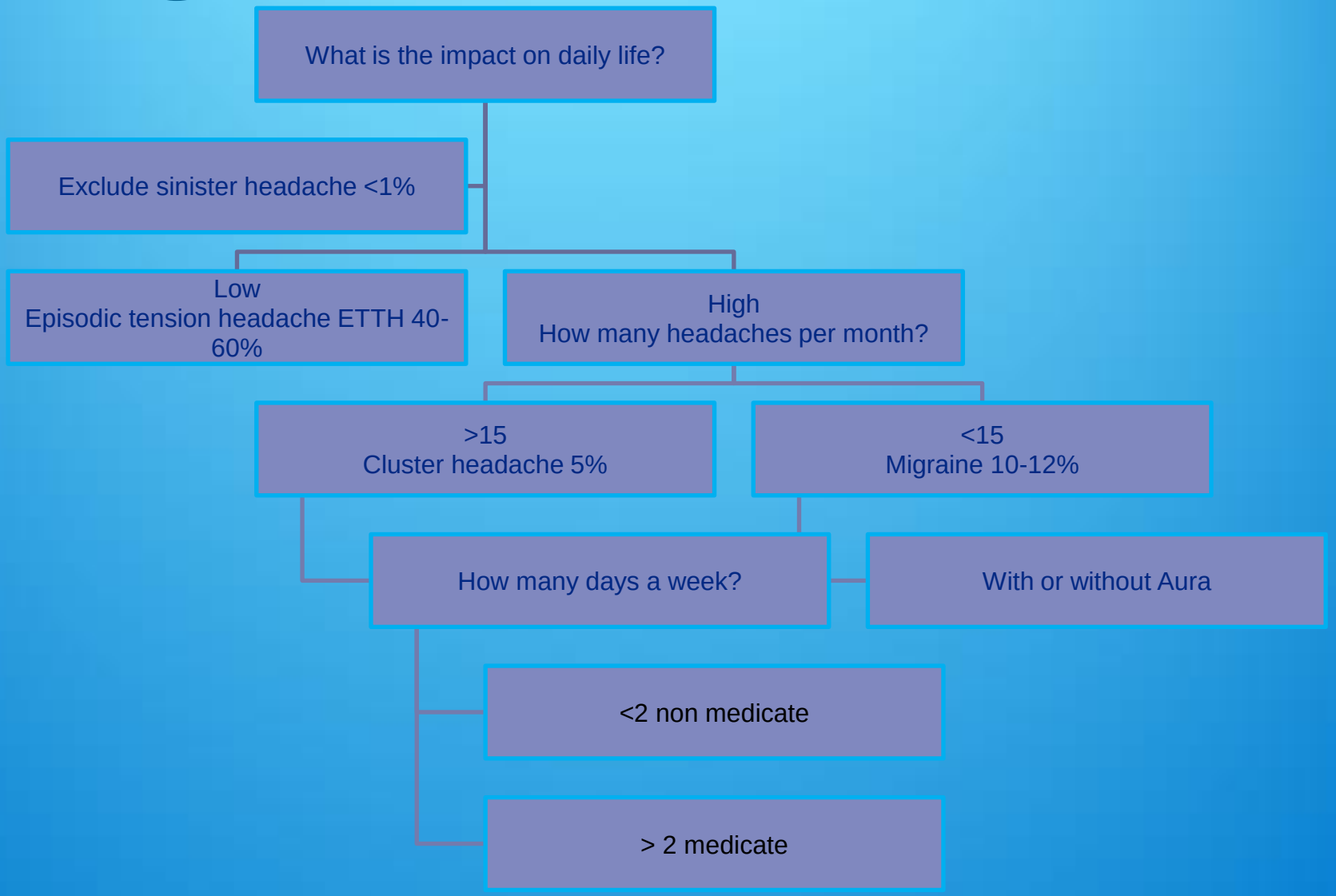
Trigeminal chronic pain

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 headaches 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 OFP 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

Idiopathic chronic OFP

TMJ pain

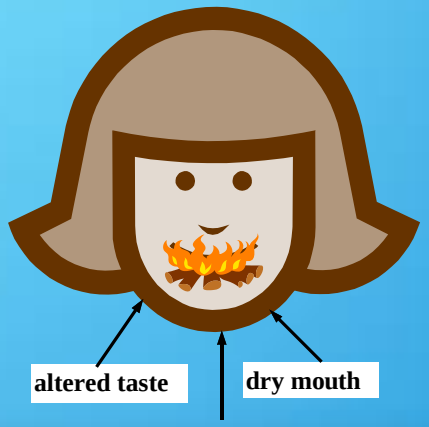
- Functional – chewing gum
- Myofacial
- Arthritides
- Derangement

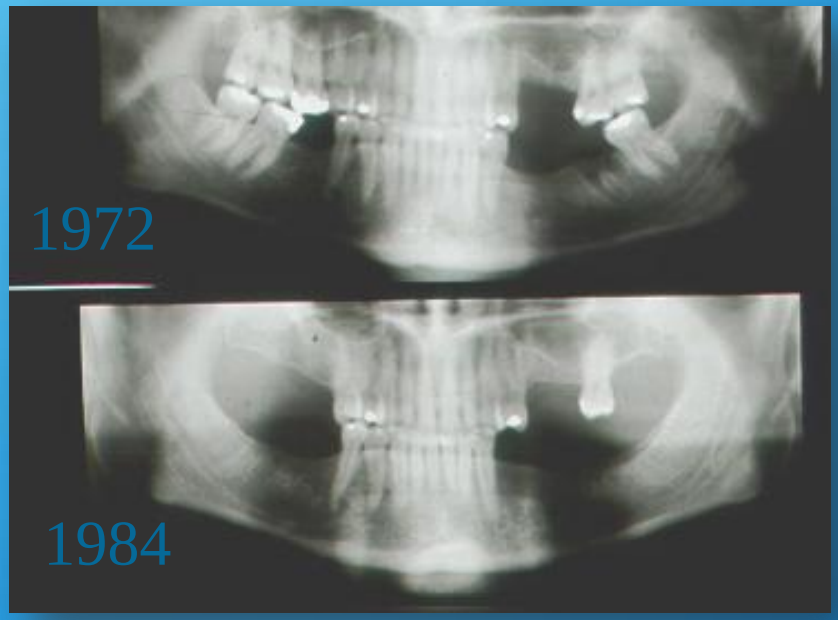
BMS

- ? neuropathy

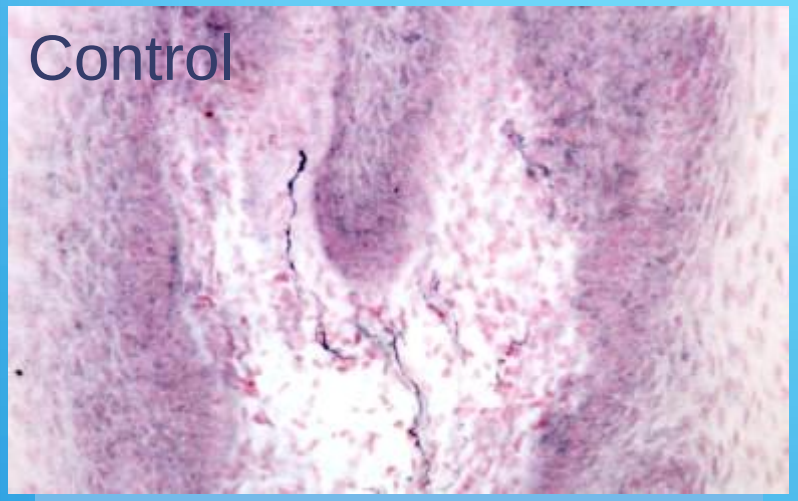
Persistent idiopathic

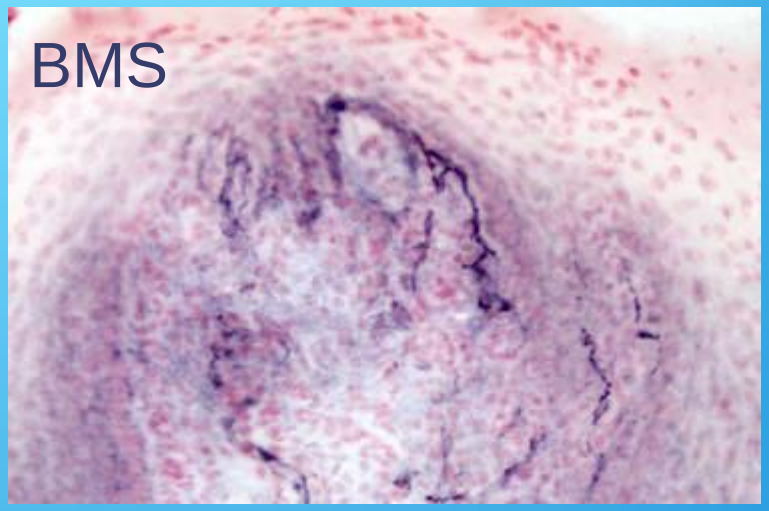
- Extraoral / facial
- Intraoral / odontalgia

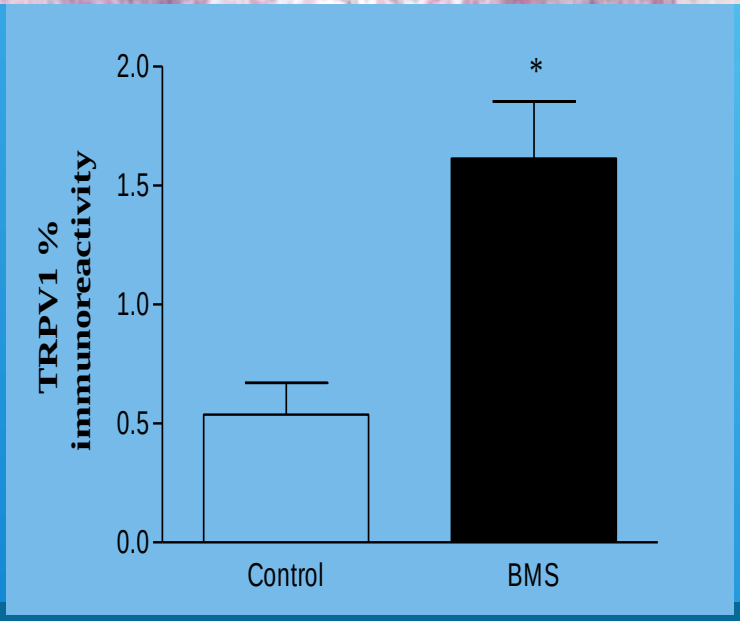




TRPV1 -IR







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

ASSESSMENT OF PAIN

Pain's 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.

Exclude systemic and local pathology

Bloods

- FBC, haematinic (folate, B12, ferritin)
- Thyroid function tests
- HBA1c
- Zinc levels
- ENAs and ANAs
- Us+Es required for contrast Gadolinium MRI scan

Exlude central pathology

Classical TN

- vascular compression

Multiple sclerosis

- MRI plaques

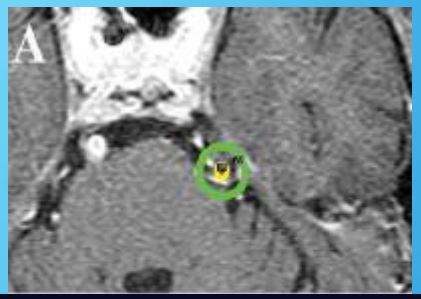
Stroke

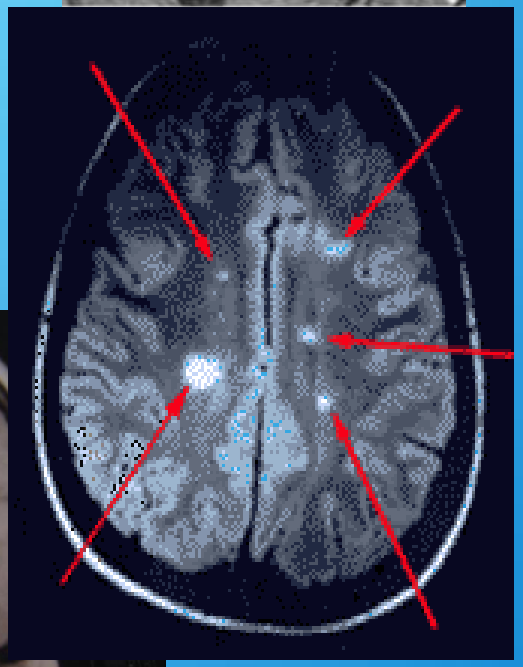
Vasculitis

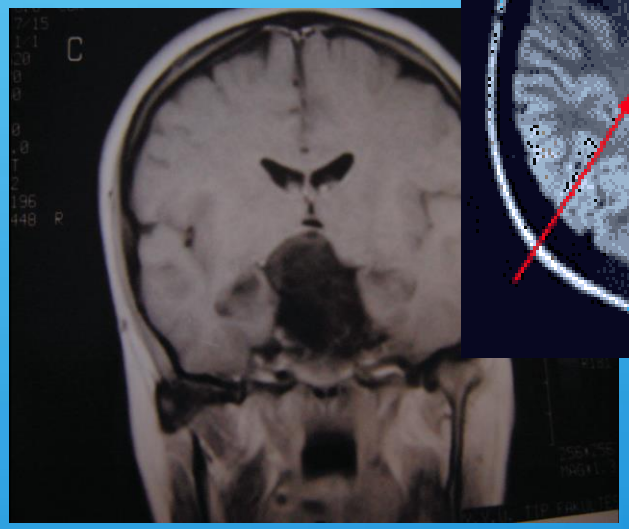
Post herpetic neuralgia

Tumours

- Meningioma

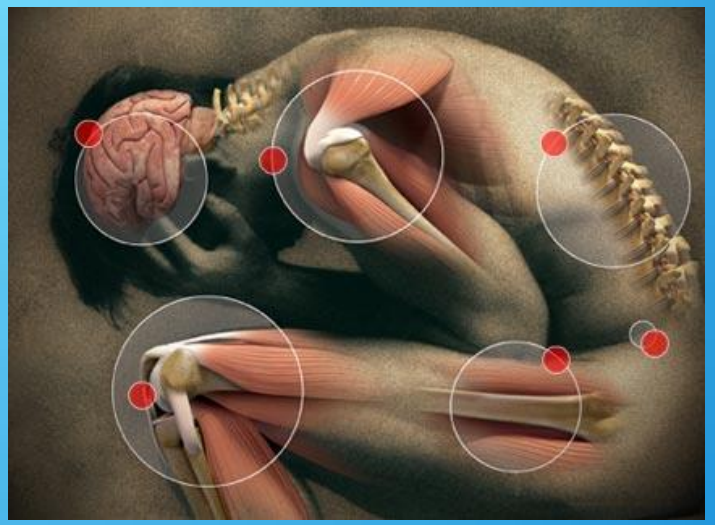




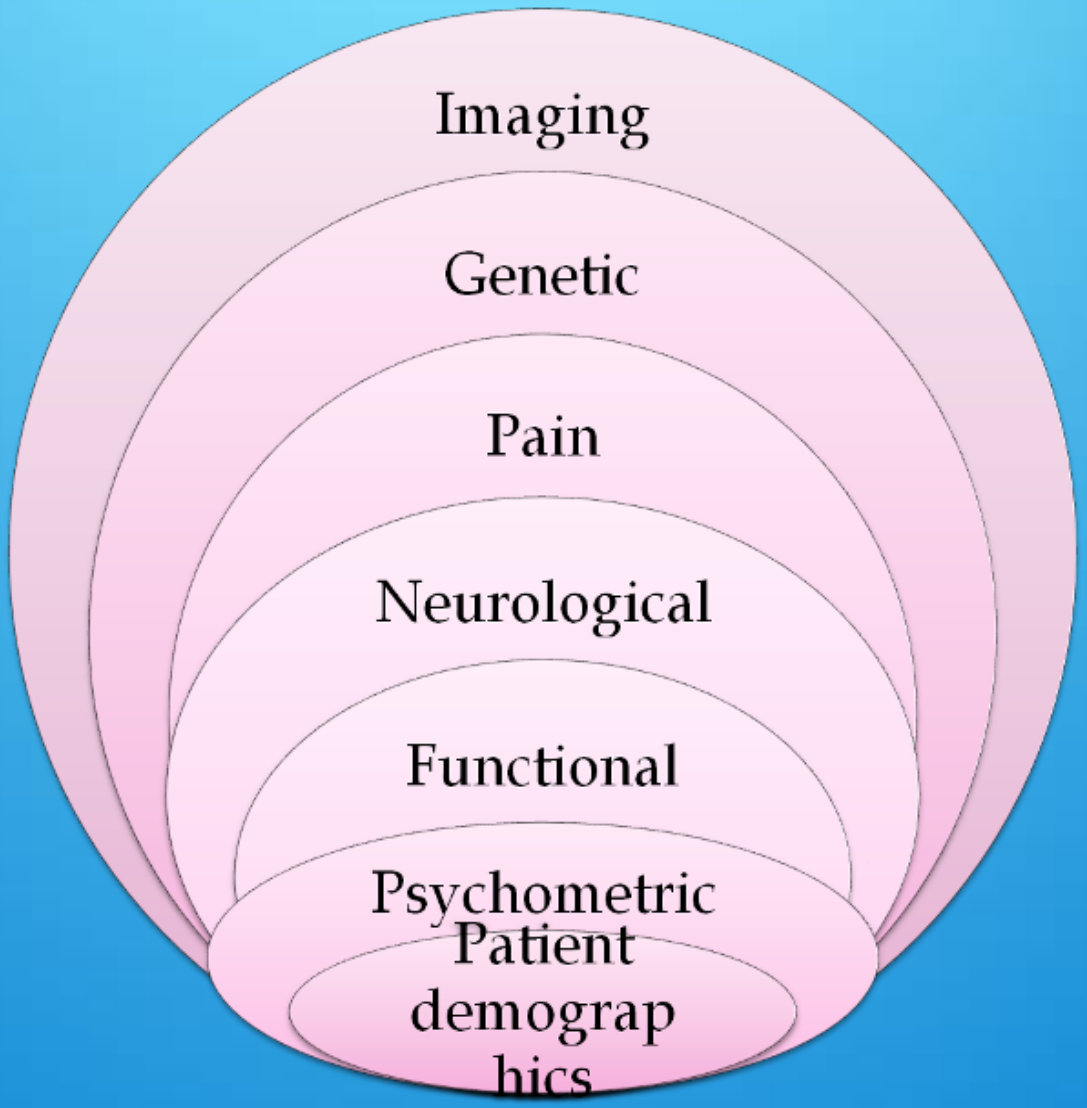


Pain assessment

- Diagnosis of pain
- Pain History
- Pain thresholds
- Subjective measurement of pain
- Indirect measurement of pain
- Objective assessment of pain

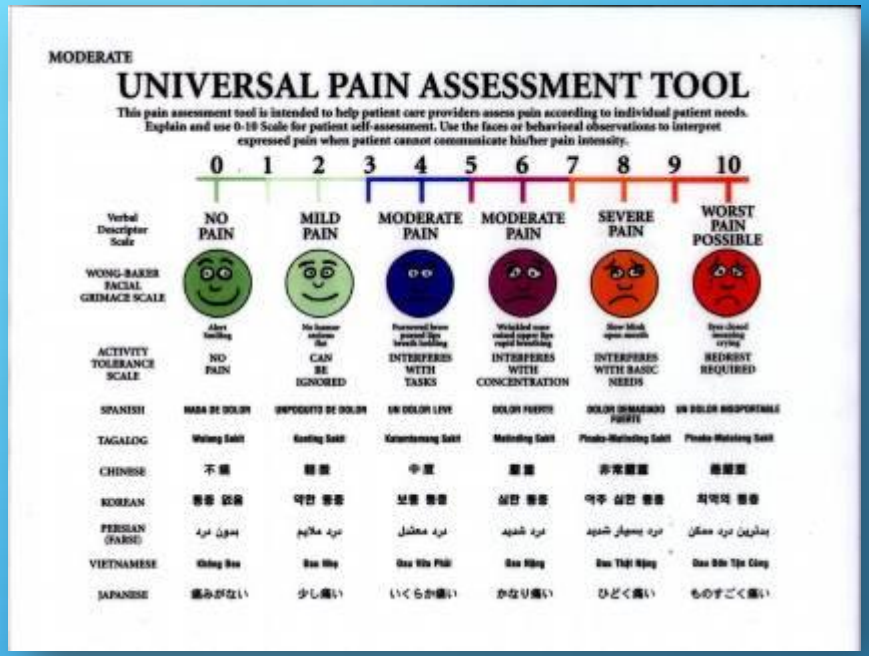


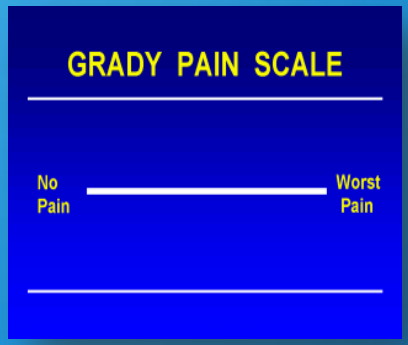
Phenotyping of patients



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



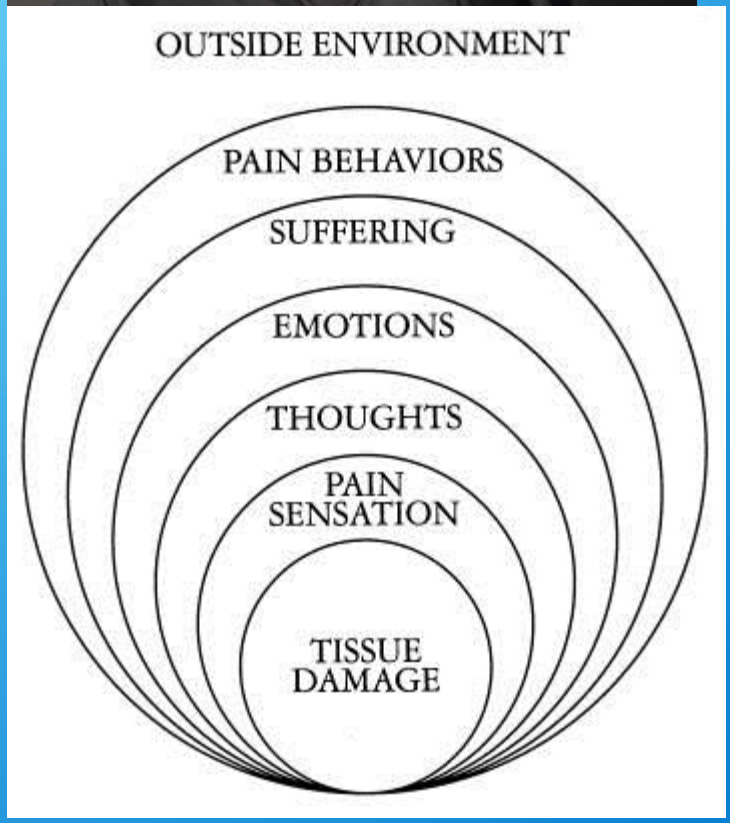


Pain history

- 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



Visual Analogue Scales

Anchors:

no pain max pain

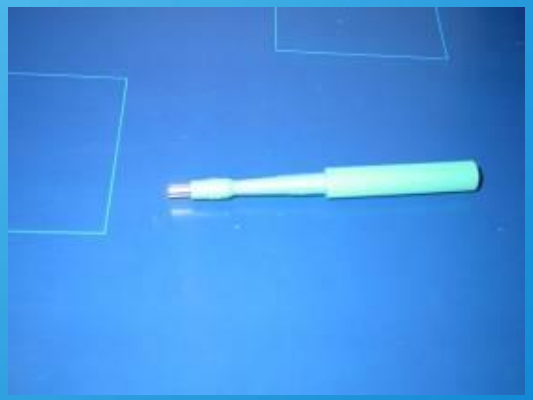
eideneurolearningblog.blogspot.com/2005_02_25...

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

10 cm line

Assessment - neuropathy

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



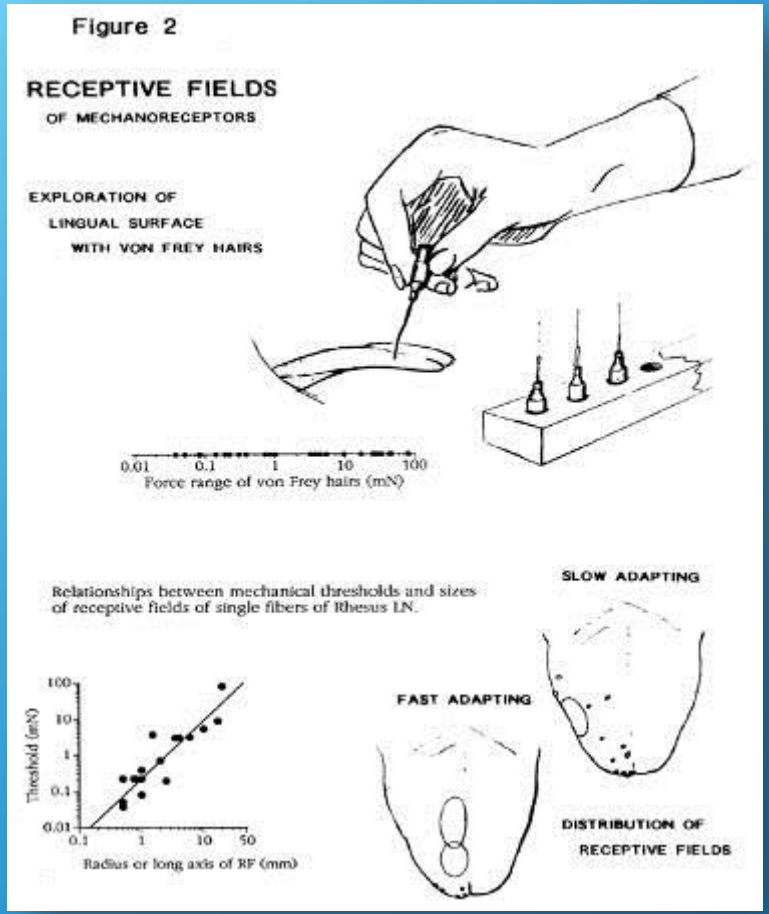
What are the problems?

With current assessment of trigeminal function

Solely mechanosensory (large fibres only)

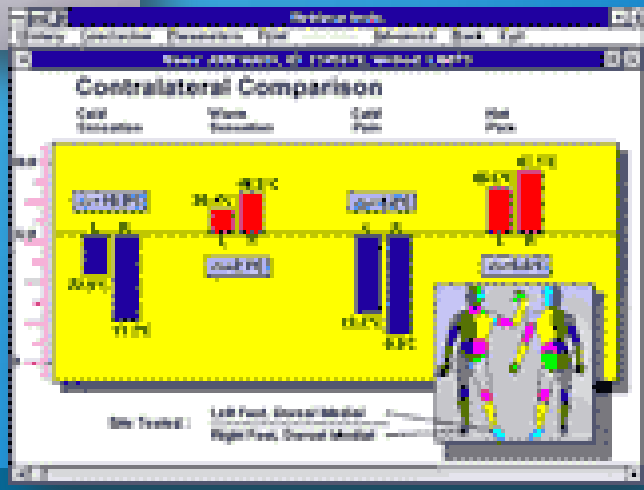
Taste tests unreliable

Pain and altered sensation often over looked

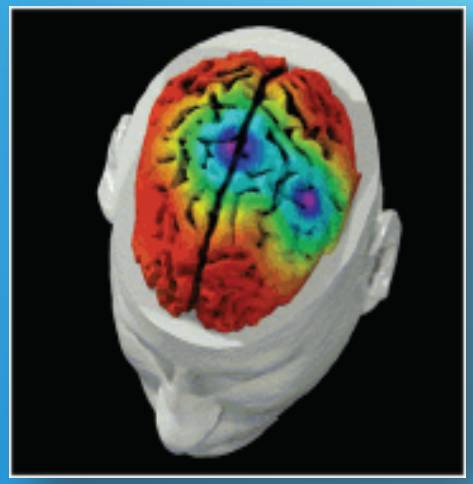


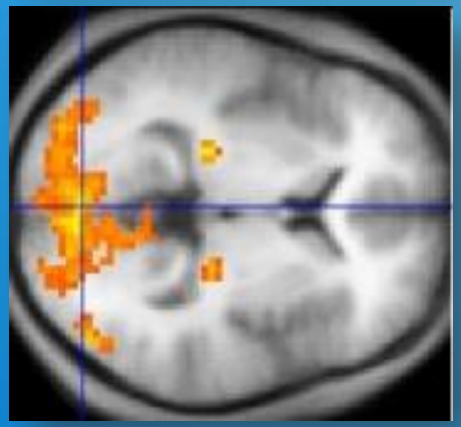
Psycho physical testing

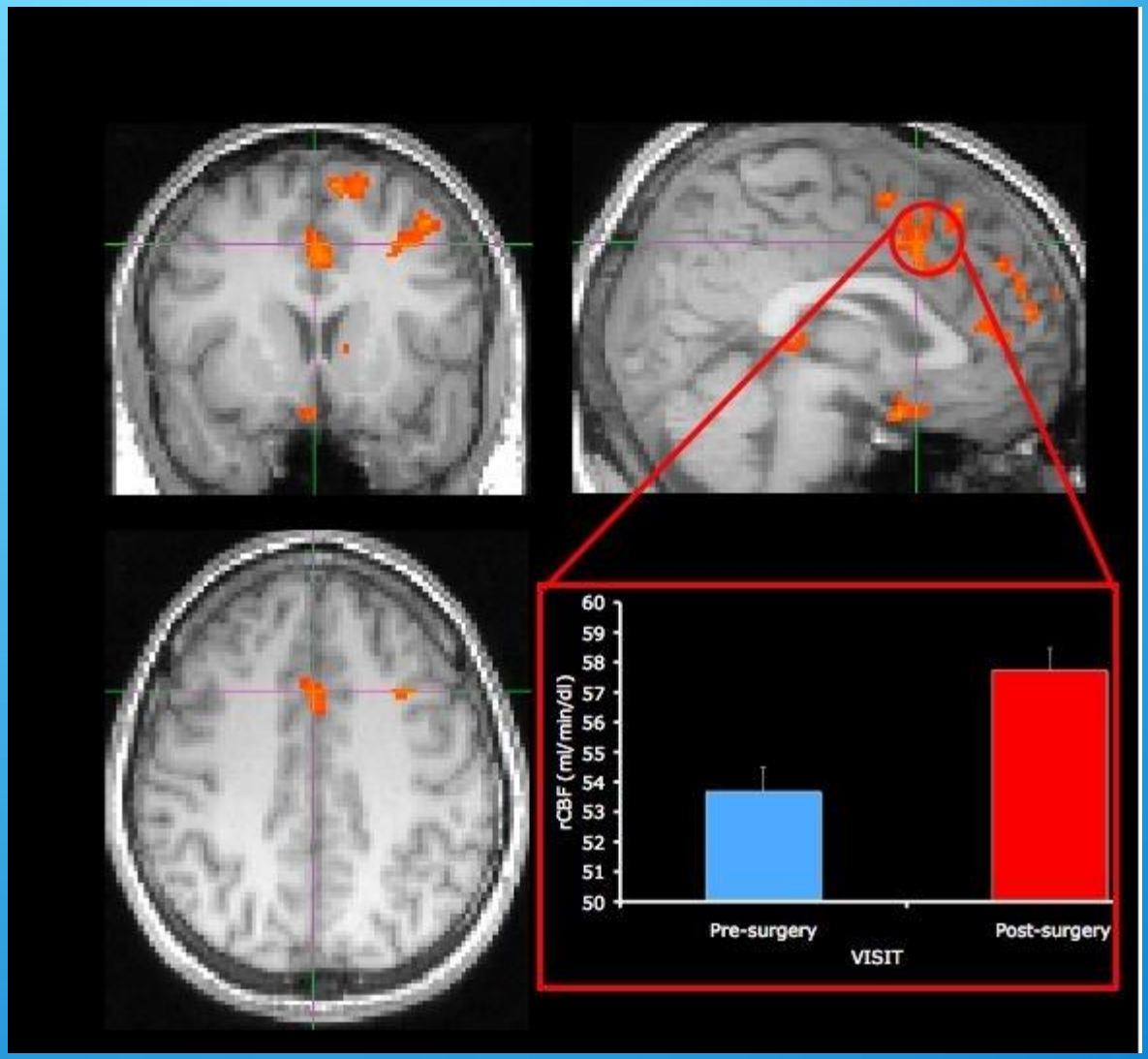
Quantitative thermo sensory testing



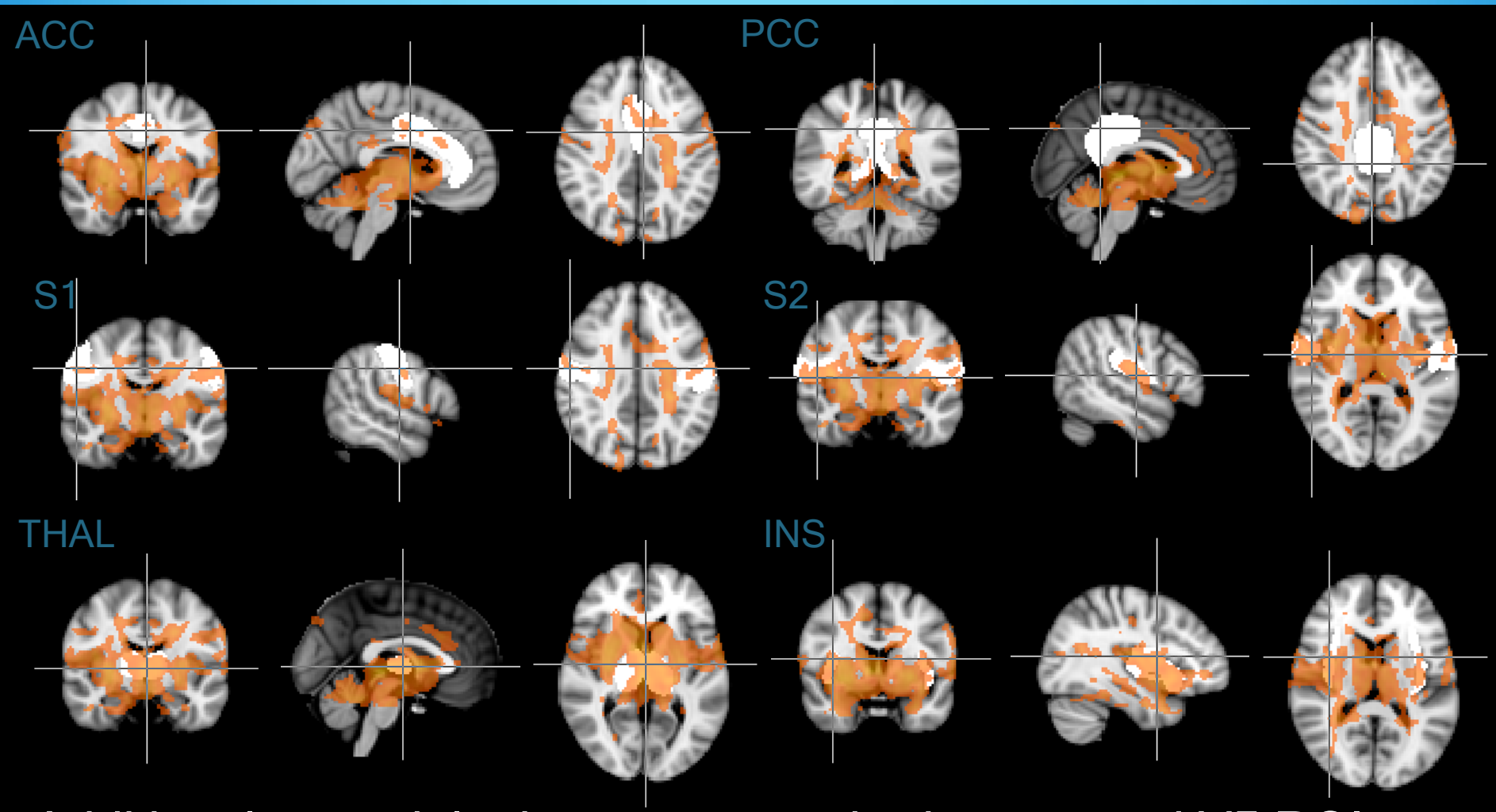
Assessment fMRI functional magnetic resonance imaging







Anatomy revisited



•Additional amygdala, hippocampus, brainstem, and V5 ROIs

MANAGEMENT OF PATIENTS AND PAIN

Manage the Pain Process

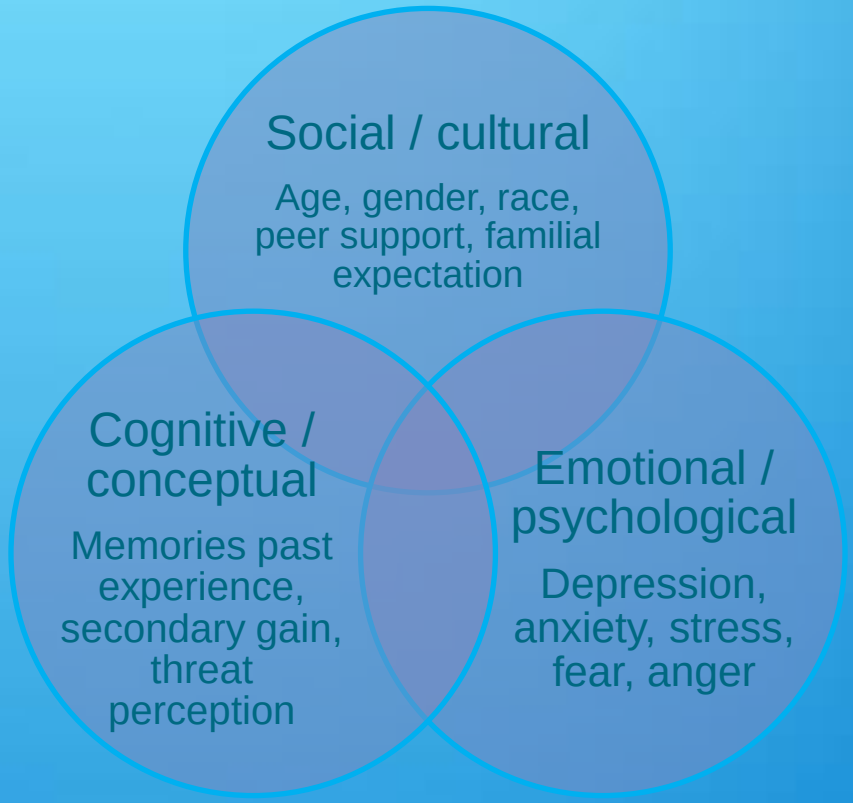
Nociception

Sensation

Behaviour

Suffering

Bio psycho social Model



Manage the Pain Process

~~Nociception~~

~~Sensation~~

~~Behaviour~~

~~Suffering~~

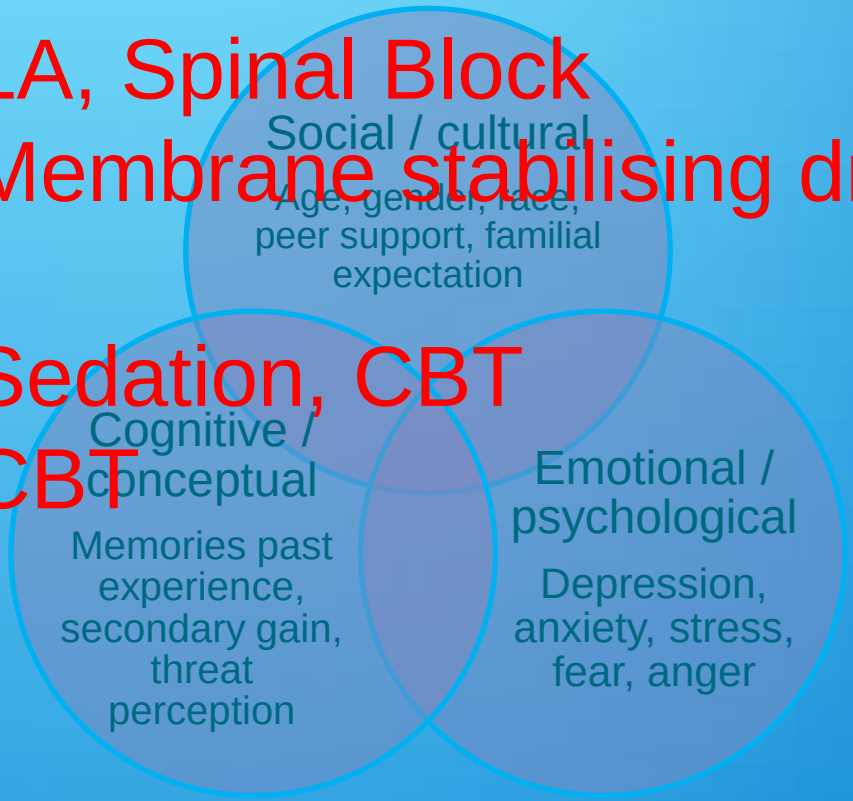
Bio psycho social Model

LA, Spinal Block

Membrane stabilising drug

Sedation, CBT

CBT



Management

Inflammatory or neuropathic pain?

Patient factors

Environment

Investigations

- Psychological
- Medical
- Surgery
- Combination

History of analgesic drugs

Opium is a Middle English word (c1100–c1500 AD) of Greek origin that passed through Latin into English.

Opium is a diminutive of the ancient Greek opos “milky juice of plant”

A Brief History of Pain Relief:

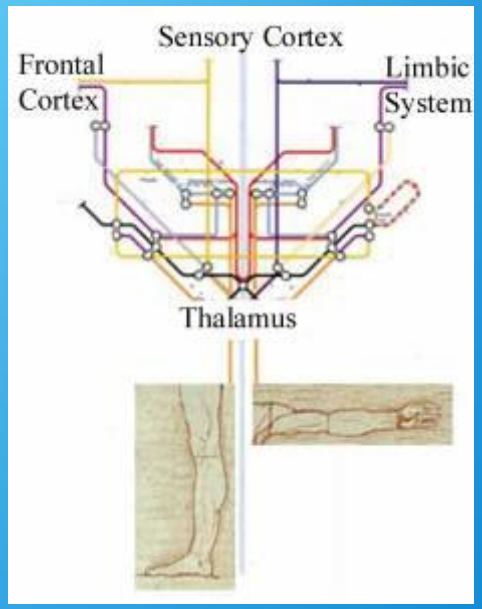
http://www.tylenolliverdamages.com/timeline.html

Management tools

Counselling	• Reassurance and explanation
Medical symptomatic therapy (pain or discomfort)	• Topical agents for pain • Systemic agents for pain
Surgical intervention	• LA diagnostic / therapeutic block Greater occipital nerve block • Cryo/glycol/thermocoag/gamma knife • MVD microvascular decompression

Management of affective /behavioural problems

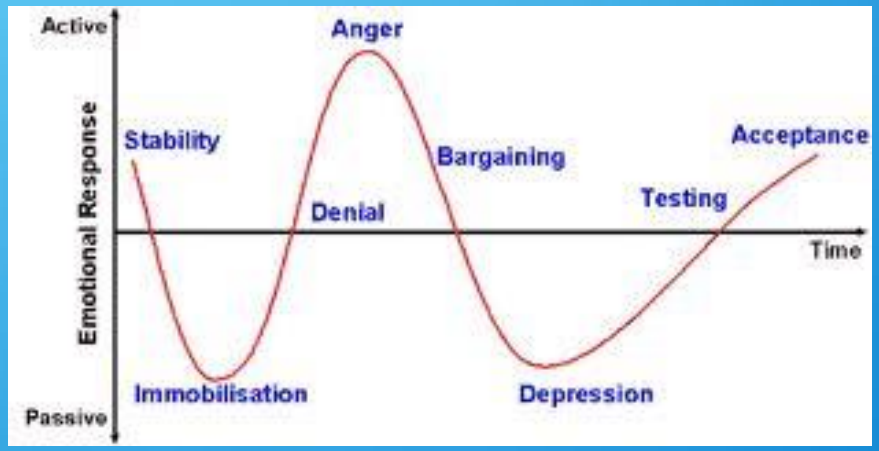
- All patients were ‘counselled’
- Liaison psychiatry
- Development of a tailored Cognitive behavioural therapy programme
- Patient website NEW
- Patient days NEW
- 50% Chronic pain sufferers are depressed Wesseley S 2010
- CBT was offered to 8% of patients



Management of affective or behavioural problems

Liaison psychiatry

Cognitive behavioural therapy



Tara Renton Premier symposium 2010

Findings:

PTSD

Victim of abuse

50% Chronic pain sufferers are depressed Wesseley S 2010

MEDICATION FOR ACUTE PAIN

Inflammatory (acute) pain

Responds to OTC analgesics

Chronic pain

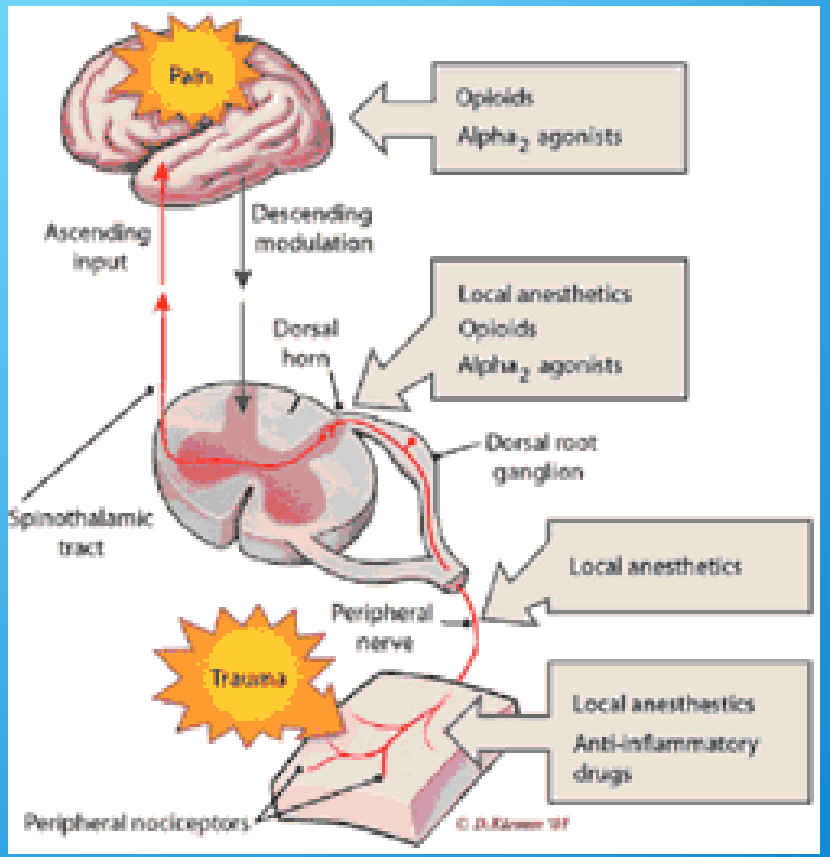
does NOT respond to OTC drugs

Guidelines (J One Day Surg 1997)

- Mild
  - Cystoscopy/peripheral surgery/grommets
    - Tylex (codeine 30mg/paracetamol 500mg QDS)
- Moderate
  - Varicose veins/adult circumcision/TOP/D+C
    - Tylex +Diclofenac (50mg QDS)
- Severe
  - Laparoscopy/hernia repair/vasectomy/testicular surgery/dental procedures
    - Tramadol QDS

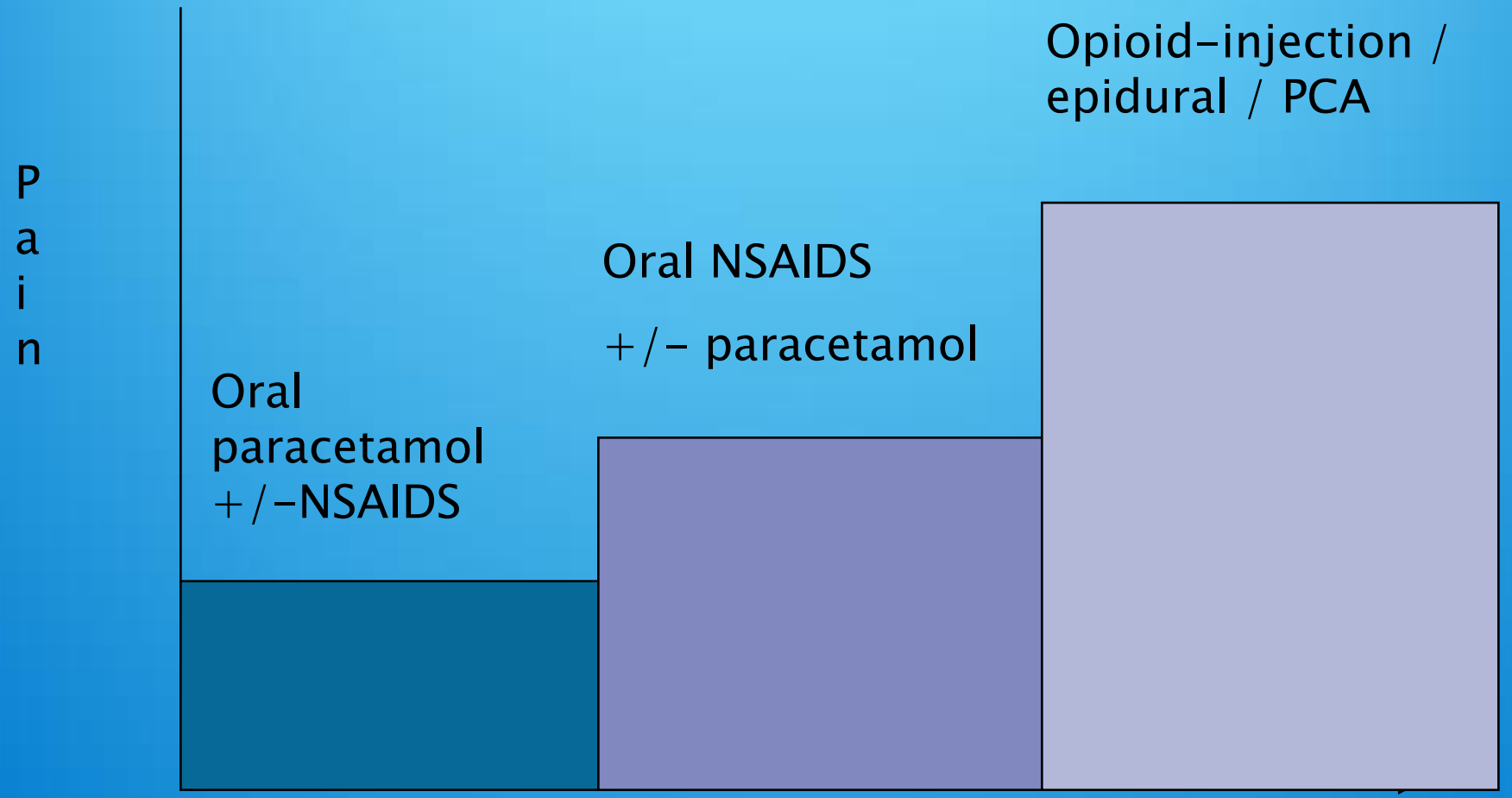
Where do drugs work?

- NSAIDS peripheral block – cyclo oxygenase
- 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



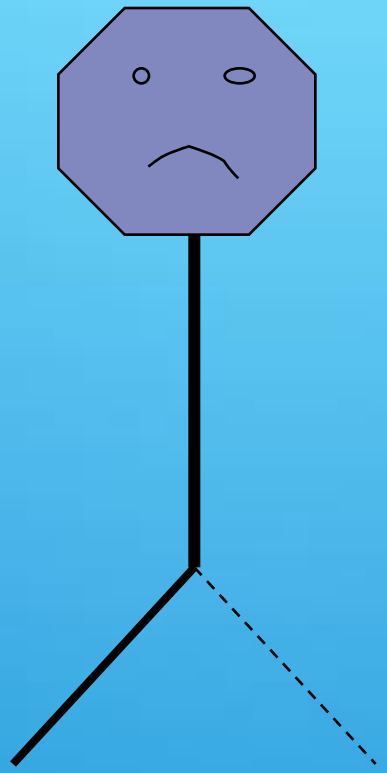
Seymour 1985

indications in dentistry mainly post op or supplemental for infections



SYDNEY STICK MAN

IASP approved model for pain therapy



1. Decrease noxious stimuli
   Correct – diagnosis
   Steroids / NSAIDS

2. Raise threshold
   Care concern counselling
   Anxiolytic/antidepressant

3. Consider opioids
   Codeine
   Morphine/methadone

4. Diagnose neuropathic pain
   Anticonvulsants+/-
   corticosteroid

DPF

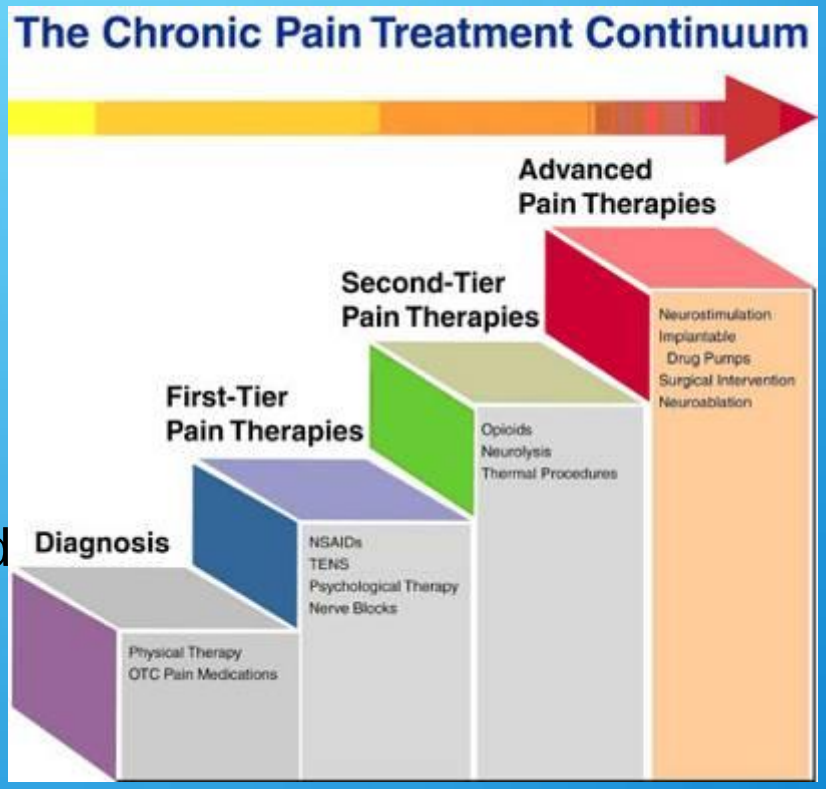
- Aspirin dispersable 300mg (1g)
- Ibuprofen tabs 200mg
  - Propionic acid derivative
- Iboprofen oral suspension 100mg/5ml
- Diflunisal tabs 250mg
  - Difluorophenyl derivative (Inc dry socket)
- Paracetamol tab 500mg
  - Acetaminophen – analine derivative
- Paracetamol sol tab 500mg
- Paracetamol oral susp 250mg/5ml
- Dyhydrocodeine tabs 30mg
- Pethidine tabs 50mg
  - Synthetic opioid

Efficacy of analgesics
expressed as need to treat (ntt)

Diclofenac	2.3
Ibuprofen 400	2.6
Morphine	3.3
Ibuprofen 200	4.4
Paracetamol + dextropropoxyphene	3.3
Paracetamol	4.8
Tramadol	5.2
Aspirin codeine	5.6
Dextroproxyphene	7.7
Tramadol	8.3
Dihydrocodeine	9.7
Codeine	10.7

Medications for Chronic pain

- Neuralgic pain
  - Oxcarbazepine
  - Neurontin pregabalin
  - Gabapentin
- Burning chronic pain
  - Nortriptyline > Amitriptyline
- 5% pts persisted with systemic med
- 18% IANI used topical medication



Chronic OFP

- LA block
  - If pain does not go then pain must be centrally mediated (not peripheral)
- Conventional analgesics do not work

Lidocaine

- Na Channel blocker
- Diagnostic blocks
- Topical patches
  - Versatis 5% Lidocaine
- IV for severe breakthrough

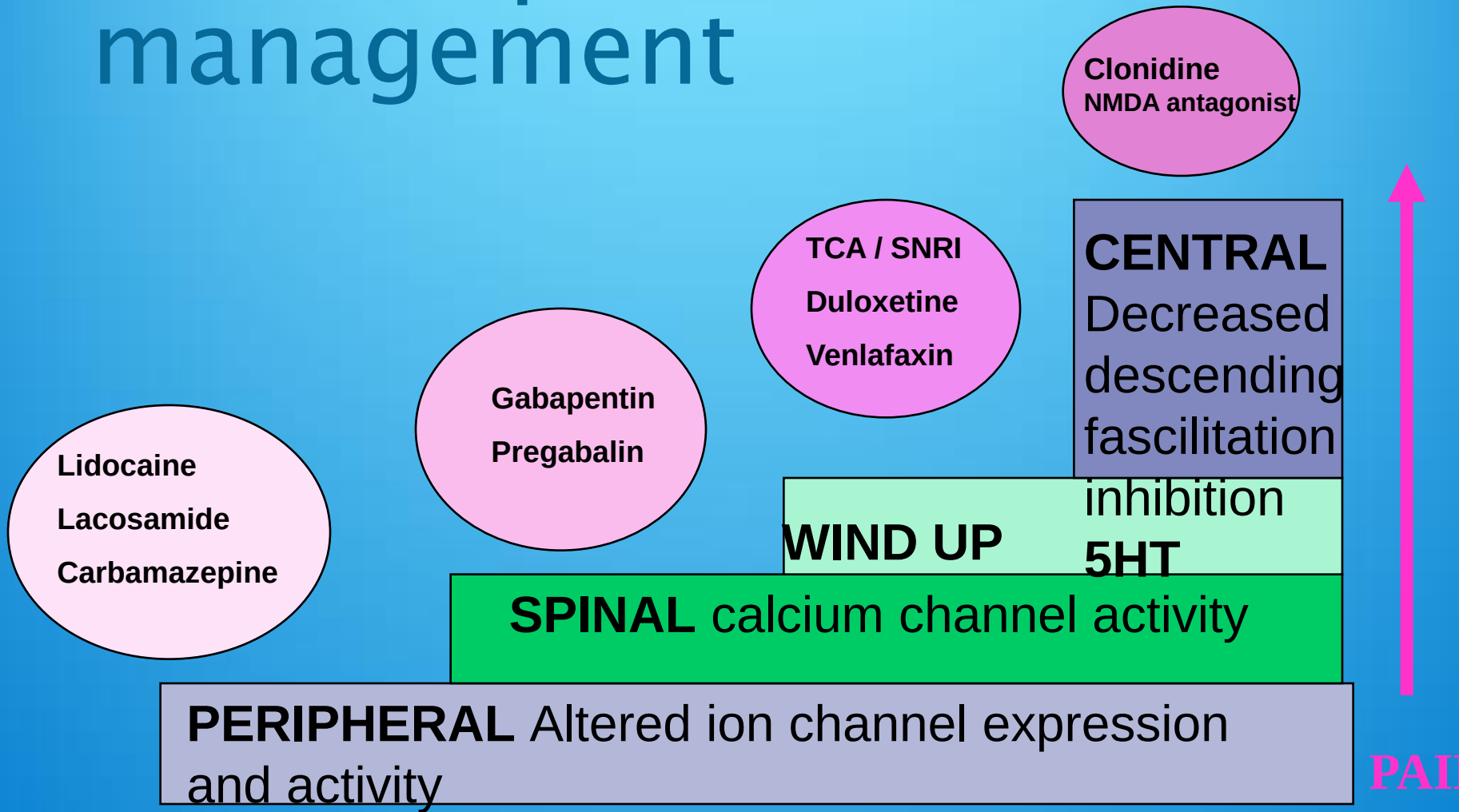
Conventional surgical management

CUT SLASH FREEZE or BURN!

Conventional surgical management

CUT SLASH FREEZE or BURN!

Chronic pain management

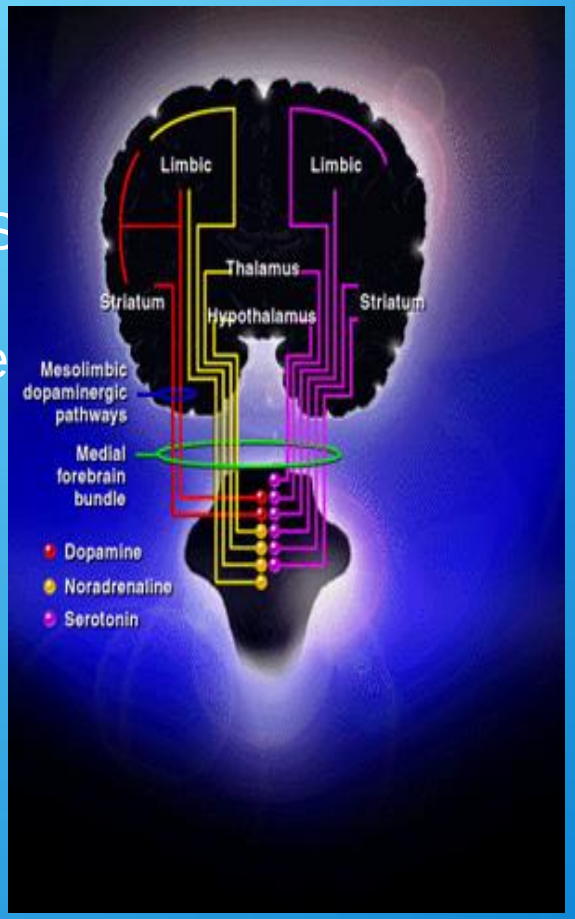


Drugs for chronic pain

- As of June 2005 only five drugs had been approved by the Food and Drug Administration to treat neuropathic pain:
- -- gabapentin, marketed by Pfizer as Neurontin, the gold-standard drug used in over 50 percent of cases and originally developed to treat depression;
- -- lidocaine, marketed by Endo Pharmaceuticals as Lidoderm, a local anesthetic;
- -- carbamazepine, originally marketed by Novartis as Tegretol, an anti-convulsant;
- -- duloxetine, an anti-depressant marketed as Cymbalta by Eli Lilly, and
- -- pregabalin, also marketed by Pfizer as Lyrica, another anti-depressant.
- Neurontin recently lost its patent protection in the United States, and a number of generic versions are now available.
- Most of these drugs need to be taken four times a day, opening a space for a pharmaceutical that requires less from the patient.

Chronic pain medication

- Local Analgesics
  - Topical / systemic
- Antidepressants
  - Selective Serotonin Reuptake Inhibitors (SSRI)
  - Selective Norepinephrine Reuptake Inhibitors (S
  - Monoamine Oxidase Inhibitors (MAOI)
  - Noradrenergic and Specific Serotonin Antidepre
- Antiepileptics
  - Tegretol –carbamazepine
  - Oxcarbazepine
  - Lacosamide
  - Alpha 2 delta ligands - Pregabalin / Gabapentin
- NMDA antagonists
  - Opioids / opiates / ketamine
- Others
  - Capsaicin
  - Alpha lipoic acid 600mg/day

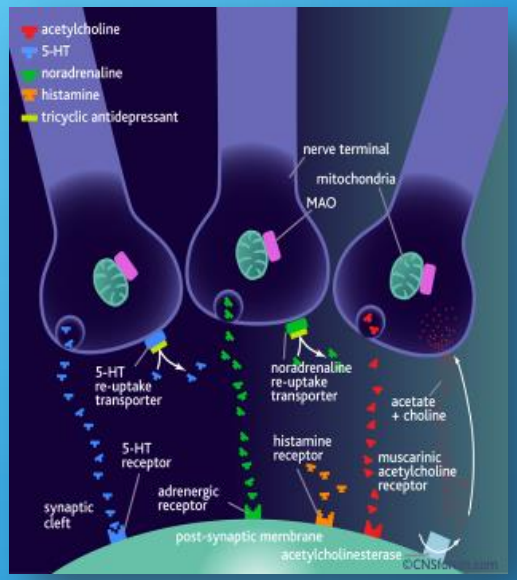


Antidepressants

- TCAs
- Selective Serotonin Reuptake Inhibitors (SSRI)
- Selective Norepinephrine Reuptake Inhibitors (SNRI)
- Monoamine Oxidase Inhibitors (MAOI)
- Noradrenergic and Specific Serotonin Antidepressants (NaSSA)

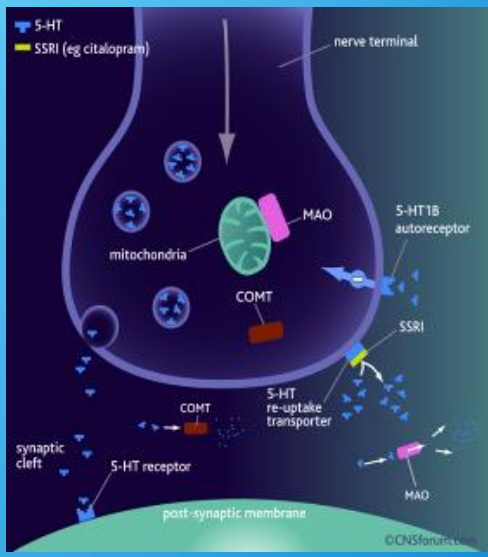
Tricyclic Antidepressants

- Tricyclic antidepressants were introduced in the late 1950s and early 1960s.
- They block the reuptake of norepinephrine by the presynaptic cell, thereby increasing its concentration in the synaptic cleft.
- Tricyclic antidepressants include:
  - nortryptiline (PamelorTM)
  - maprotiline (LudiomilTM)
  - desipramine (NorpramineTM)
  - amitryptiline (ElavilTM)
  - clomipramine (AnafranilTM)
  - imipramine (TrofranilTM)
- Side effects
  - affect heart rate and blood pressure
  - postural hypotension
  - Tachycardia (rapid heart rate)
  - dry mouth, urinary retention and blurry vision
  - Physicians must monitor the patient closely for toxic side effects.
  - Tricyclic antidepressants are nonselective inhibitors of norepinephrine reuptake because their chemical structures look like norepinephrine.



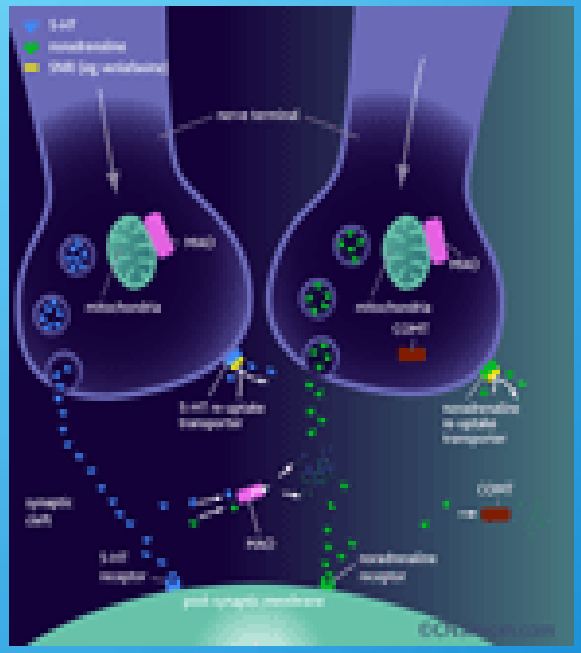
Selective Serotonin Reuptake Inhibitors (SSRI)

- introduced in the mid-1980s. SSRIs block the transport of serotonin back into the presynaptic cell, increasing stimulation of the postsynaptic cells.
- SSRIs include the following drugs:
  - fluoxetine (ProzacTM)
  - paroxetine (PaxilTM)
  - sertraline (ZoloftTM)
  - fluvoxamine (LuvoxTM)
  - citalopram (CelexaTM)
  - escitalopram (LexaproTM)
- some patients may experience more side effects with one type of SSRI than with another. Most of the time, patients have to take antidepressants more than once per day.
- fluoxetine has a longer half-life -- it remains in the body longer, so patients can usually take it once a day. This lowers the chance of missing a dose. At high doses, paroxetine and sertraline will interfere with dopamine and serotonin neurotransmission



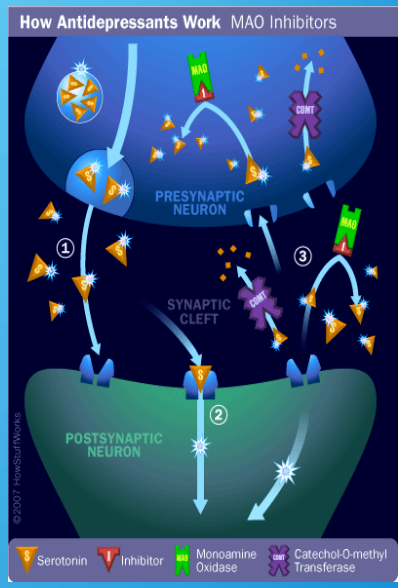
SNRIs

- Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)
  introduced in the mid-1990s
- block the reuptake of both serotonin and norepinephrine by binding to the transporters of these neurotransmitters on the presynaptic cell.
- SNRIs include:
  - bupropion (WellbutrinTM) -- blocks dopamine and norepinephrine reuptake as well
  - duloxetine (CymbaltaTM)
  - venlafaxine (EffexorTM)
- side effects of these drugs are similar to, but less than, those of SSRIs. Bupropion and duloxetine, in particular, have minimal side effects in the areas of sexual dysfunction and weight gain.



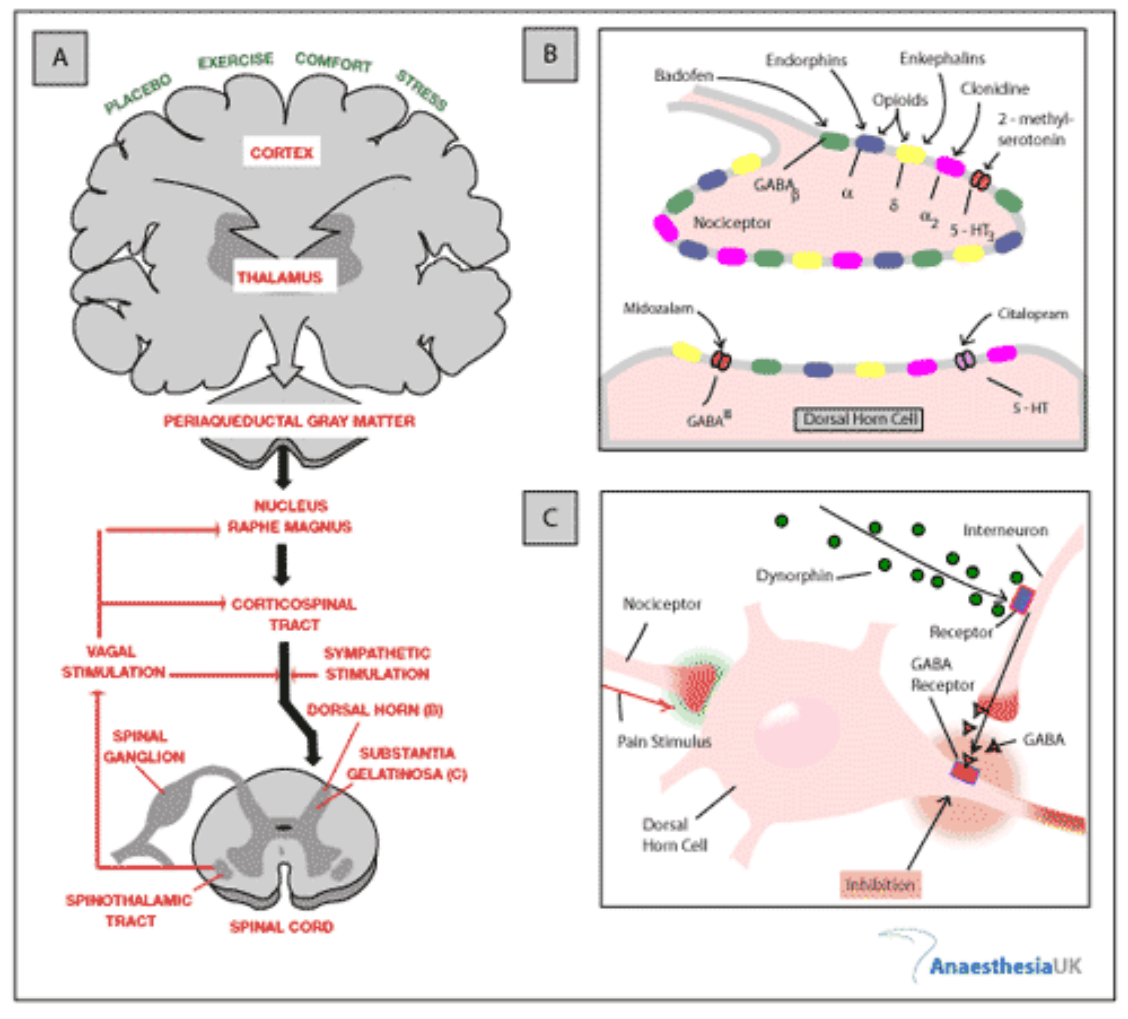
Monoamine Oxidase Inhibitors (MAOI)

- An enzyme called monoamine oxidase can degrade serotonin and norepinephrine in the synaptic cleft and presynaptic cell. MAOIs block this degradation, increasing the concentration of the neurotransmitters.
- MAOIs include:
  - phenelzine (NardilTM)
  - tranylcypromine (ParnateTM)
  - selegiline (EldeprylTM)
  - isocarboxazid (MarplanTM)
  - moclebemice (ManerixTM)
- can interfere with norepinephrine - cardiovascular side effects.
- patients must limit their consumption of foods containing tyramine because the drugs interact with tyramine to cause hypertension



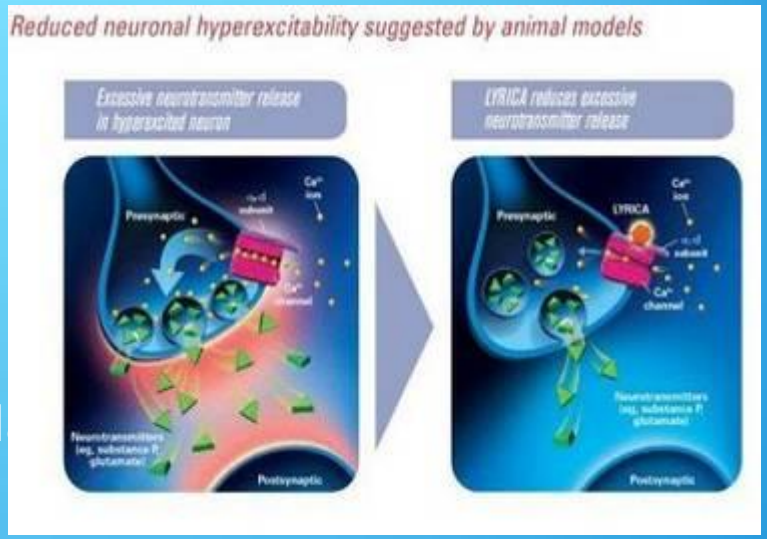
- Tyramine can be found in foods like soy sauce, sauerkraut, chicken and beef livers, aged cheese, sausage, cured meat and fish, yogurt, raisins, figs and sour cream. Patients also have to refrain from consuming alcohol when on these antidepressants. Because of these interactions, doctors do not prescribe this class of antidepressants as frequently as others.

Migraine


A
PLACEBO
EXERCISE
COMFORT
STRESS
CORTEX
THALAMUS
PERIAQUEDUCTAL GRAY MATTER
NUCLEUS RAPHE MAGNUS
CORTICOSPINAL TRACT
VAGAL STIMULATION
SYMPATHETIC STIMULATION
DORSAL HORN (B)
SPINAL GANGLION
SUBSTANTIA GELATINOSA (C)
SPINOTHALAMIC TRACT
SPINAL CORD
B
Baclofen
Endorphins
Enkephalins
Opioids
Clonidine
2 - methyl-serotonin
GABA$_B$
α
δ
α$_2$
5 - HT$_3$
Nociceptor
Midazolam
Citalopram
GABA^B
Dorsal Horn Cell
5 - HT
C
Interneuron
Dynorphin
Nociceptor
Receptor
GABA Receptor
GABA
Pain Stimulus
Dorsal Horn Cell
Inhibition
AnaesthesiaUK

Antiepileptics

- Tegretol –carbemazepine
- Oxcarbazepine
- Pregabalin
  - 75mg/day=placebo 300=600mg /d
- Gabapentin
- Topiramate
- Lacosamide
- Clonazepam is a benzodiazepine
- NMDA antagonists ?
  - Opioids / opiates / ketamine / methadone
- Others
  - Capsaicin



Problems with medication for pain

- Still only 40% of patients get 50% pain relief with best drugs
- Side effects for example Pregabalin
  - Dizziness, somnolence, sexual difficulties, confusion
  - Weight gain TCA GP PGB Dulox
- Elderly people more sensitive to postural hypotension
- CV disease avoid TCAs and carbamazepine
- Epilepsy avoid TCAs
- Bipolar disorder avoid TCA
- Renal impairment avoid gabapentin

Specific management of orofacial pain

- Evidence based where possible

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	

Management of chronic orofacial pain

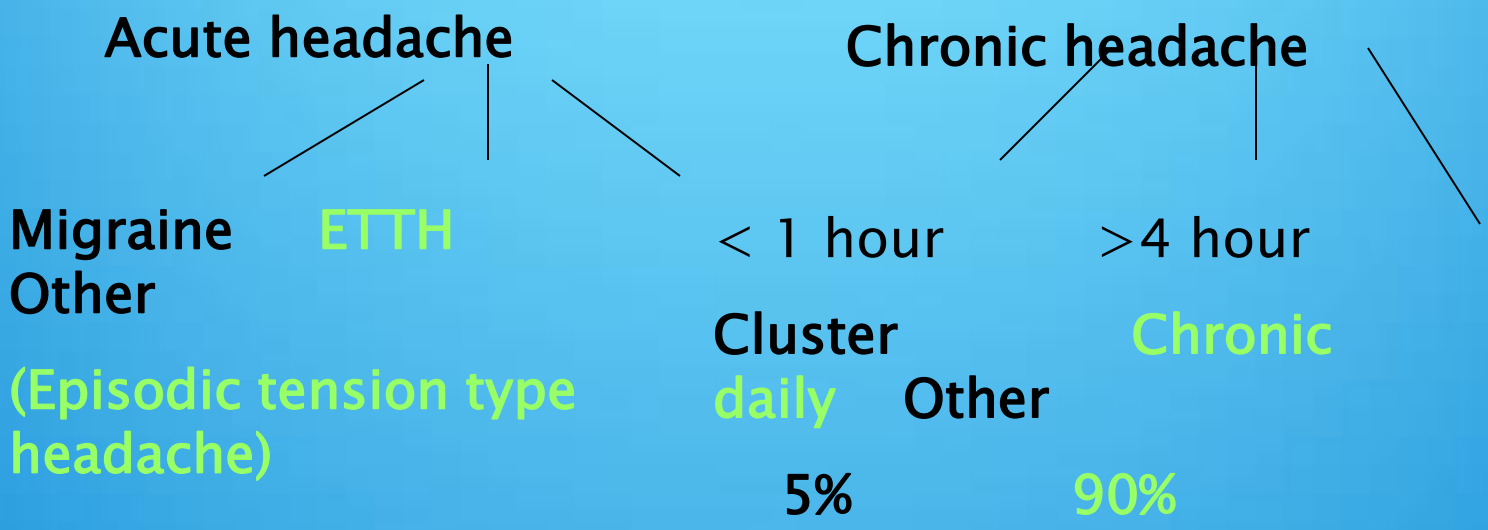
- Neurovascular &Tension type
  - Tension type headache
  - Migraine
  - Cluster headache
  - Giant cell arteritis
- Neuralgia
  - Trigeminal neuralgia
  - Post herpetic neuralgia
  - Post traumatic sensory nerve injury
- Persistent idiopathic
  - TMJ arthromyalgia
  - BMS
- Counselling
  - CBT
- Drugs
  - Opiate/opioids
  - TCAs Antidepresants
    - Tricyclic antidepressants
  - SNRIs
  - Anticonvulsants
- Topical local analgesia
- Other componds
  - Capsaicin

Management of headaches

The vast majority of episodic, impactful headaches reported by patients are caused by migraine

Intermittent
mild-to-moderate migraine
(+/- aura)
Intermittent
moderate-to severe migraine
(+/- aura)
Aspirin/NSAID (large dose)
Aspirin/paracetamol plus anti-emetic
Oral triptan
Nasal spray/subcutaneous
triptan

Chronic OFP
Neurovascular & Tension type Headache



IHS Classification of Headaches

- Tension Type Headaches
- Migraine
- Cluster Headache

Exclude sinister headaches

- Subarachnoid haemorrhage - recent trauma LoC
- Cranial arteritis
- Tumour 1%
- >50 yrs
- New-onset, acute headaches associated with other symptoms
  - e.g. rash, neurological deficit, vomiting, pain/tenderness, accident/head injury, hypertension
  - Neurological change/deficit does not disappear when the patient is pain-free between attacks
  - Develop algorithm for sinister headaches
- Dowson AJ, Cady RC. Rapid Reference to Migraine 2002.

Classification of Chronic orofacial pain

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	Lingual inferior alveolar nerve injuries	

Post ophthalmic herpes zoster – hyperaemia and corneal scarring

Post Herpetic Neuralgia

- 20% of patients (60%>50yrs) progress to neuropathic pain after Shingles caused by a reactivation of the varicella-zoster virus (VZV).
- In the trigeminal system most commonly V1 and V2
- If patient is <40 years check immuno status (15 times higher in HIV-infected patients)
  - If caught early treat with high dose ant-ifungals
    - Acyclovir (Zovirax)†800 mg orally five times daily for 7 to 10 day 10 mg per kg IV every 8 hours for 7 to 10 days
    - Prednisone 30 mg orally twice daily on days 1 through 7; then 15 mg twice daily on days 8 through 14; then 7.5 mg twice daily on days 15 through 21
  - Ramsay hunt syndrome HZ of geniculate ganglion (facial nerve, CT)

Management of Post herpetic neuralgia

- High dose steroids and antivirals (Acyclovir) during acute infection phase
  - If caught early treat with high dose antifungals
    - Acyclovir (Zovirax)†800 mg orally five times daily for 7 to 10 day 10 mg per kg IV every 8 hours for 7 to 10 days
    - Prednisone 30 mg orally twice daily on days 1 through 7; then 15 mg twice daily on days 8 through 14; then 7.5 mg twice daily on days 15 through 21
    - Amitriptyilne

Management traumatic nerve injury

- Counselling
  - CBT
- Medical
  - Antidepressants
    - Tricyclic antidepressants
      - Amitriptyline
      - Nortriptiyine
  - Anticonvulsants
    - Carbamazepine
    - Gabapentin
    - Pregabalin
- Surgery early repair / late exploration repair
  - 90% patients feel as though surgery is worthwhile (Robinson PP et al., 2003)

Trigeminal Neuralgia

IASP defines trigeminal neuralgia as

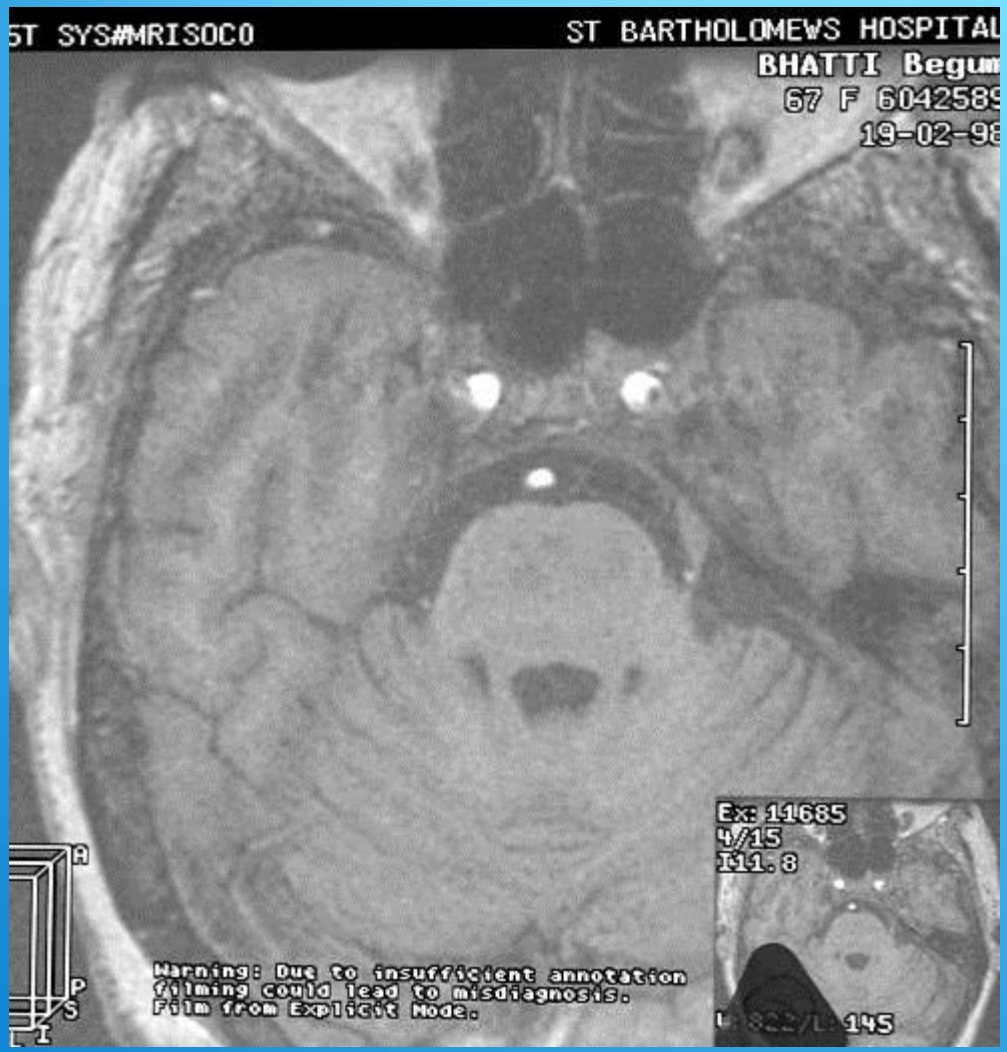
" a sudden, usually unilateral, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve".

Trigeminal Neuralgia

- Character
  - Flashing, shooting, sharp, unbearable
- Severity
  - Moderate to severe
- Site, radiation
  - Distribution of trigeminal nerve
- Duration, periodicity
  - Bouts last for seconds, pain free periods
- Provoking factors
  - Light touch, eating, talking
- Relieving factors
  - Avoid touch, anticonvulsants
- Associated factors
  - Trigger areas, weight loss

TN Investigations

- MRI – patients under 40 years
- to exclude multiple sclerosis and to assess if micro vascular compression
- CT - tumours of posterior fossa
- Haematological tests
- Biochemical tests
- Neurological – sensory testing and hearing



MRI scan

Diagnosis and differential diagnosis of trigeminal neuralgia

Zakrzewska JM.
Clin.J.Pain 2002;18:14-21

Management of TN

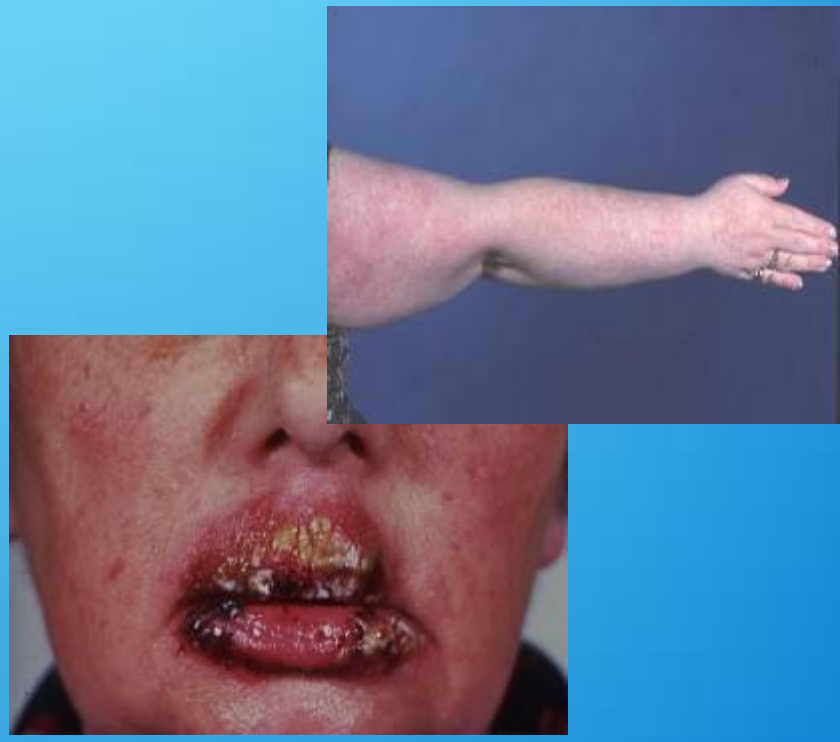
- If patient under 40 years consider MS
- Patient presenting with sudden onset neuralgia
- You need to exclude
  - Space occupying lesions (always examine cranial nerve excluding 1 and 8
  - Demyelination plaque (MS) using Gadolinium = T2 enhancement MRI
  - Vascular compromise of Vth ganglion
  - (Devor)

Carbamazepine - Tegretol

- First line treatment
- 70% of patients will respond with a reduction of pain
- Use doses from 300-800mg daily – four times daily
- Increase doses slowly
- Drug interactions common
- Failure often due to increased severity of pain
- Use retard formulation at night

Carbamazepine (CBZ)

- All patients will get side effects
- Drowsiness/tiredness
- Dizziness
- Zombie feeling
- Diplopia
- Ataxia
- Allergy 7%



RCTs in Trigeminal Neuralgia

- Drugs:

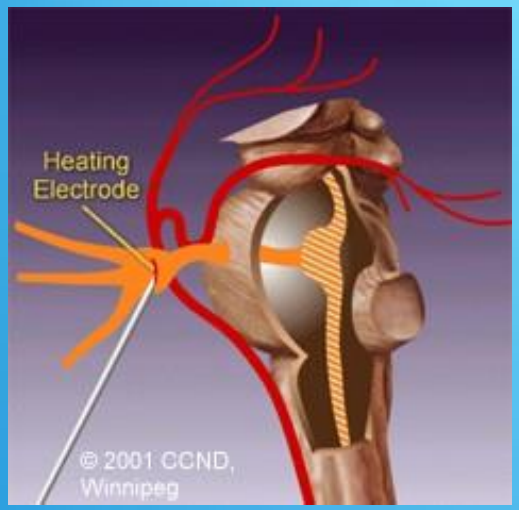
carbamazepine	effective
lamotrigine	likely to be beneficial
baclofen	likely to be beneficial
pimozide	trade off benefit /harm
tizanidine	unknown effectiveness
proparacaine	unlikely to be beneficial
tocainide	harmful

- Surgery:
  - Peripheral streptomycin not beneficial
  - Microvascular decompression most effective

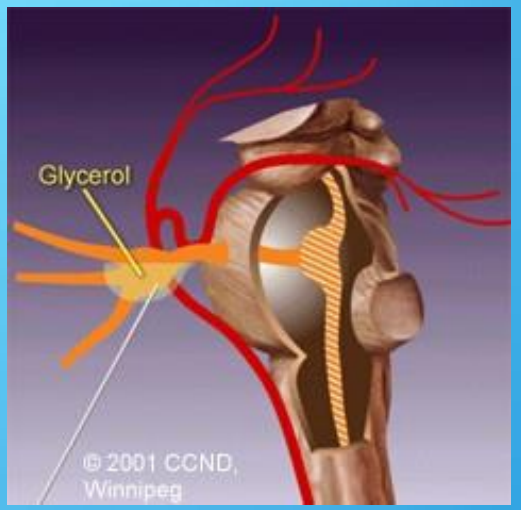
Ideal TN Surgery

- Widely available in many centres
- Minimally invasive – day stay or short admission
- Does not require a highly trained surgeon
- Immediate and complete relief of the attacks
- Allows all medications to be stopped
- Curative or low recurrence rate
- Causes no systemic complications e. g. hearing, stroke
- None or few local side effects
- Restores quality of life
- Requires no long term follow up
- Repeatable with no added risks
- Cost effective

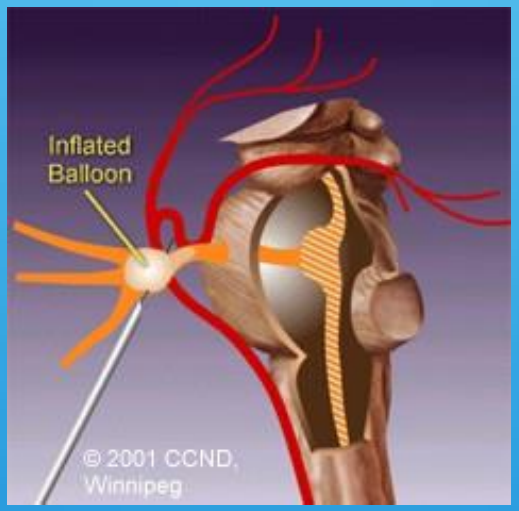
Obliteration of the Gasserian Ganglion procedures



Radiofrequency rhizotomy

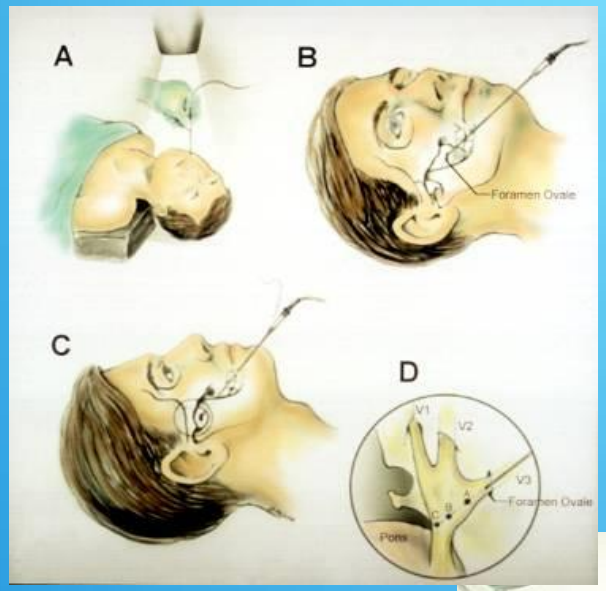


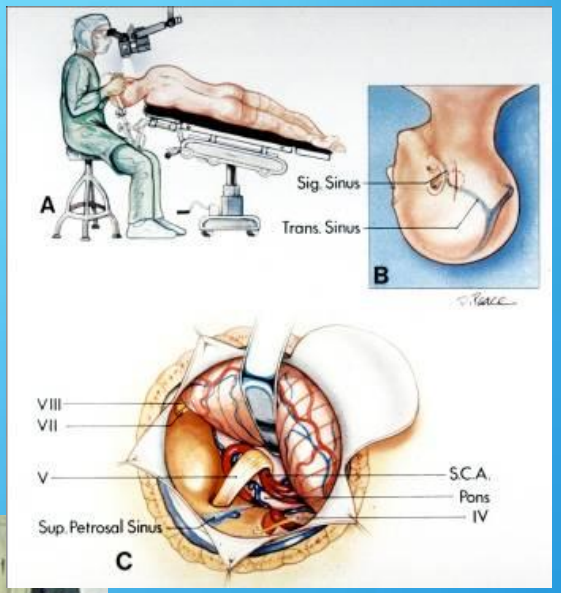
Glycerol rhizotomy

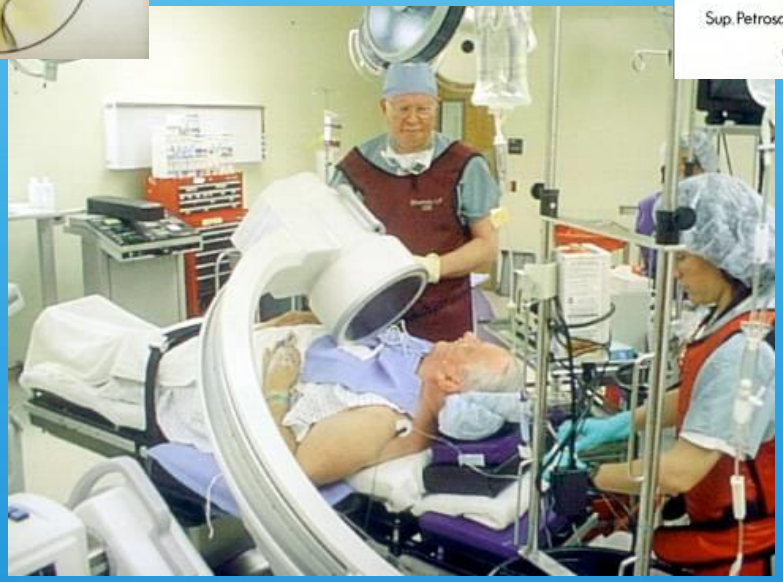


Balloon compression

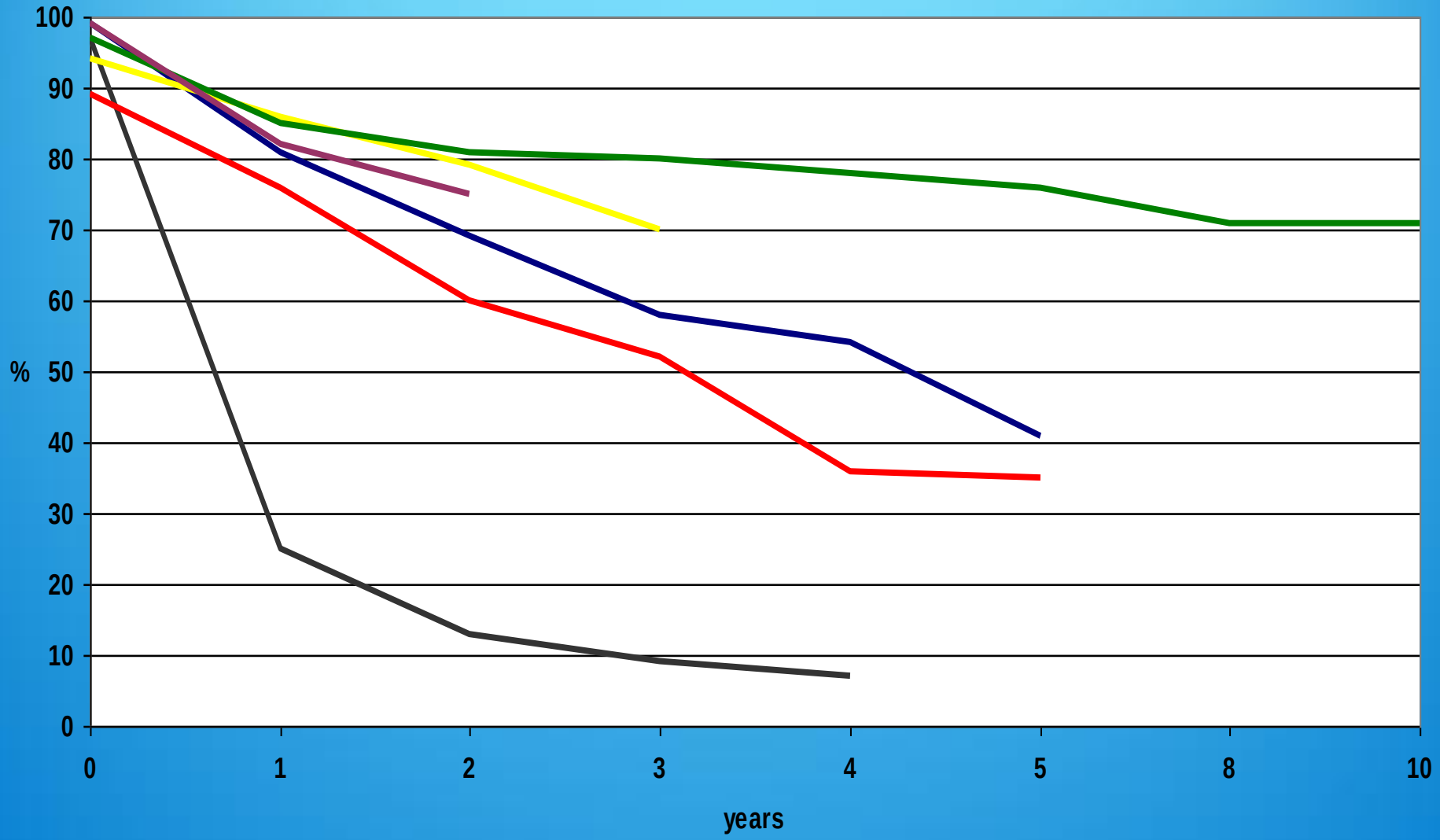
Obliteration of Gasserian ganglion OR MVD ?







Probability of being pain free after surgery for trigeminal neuralgia.

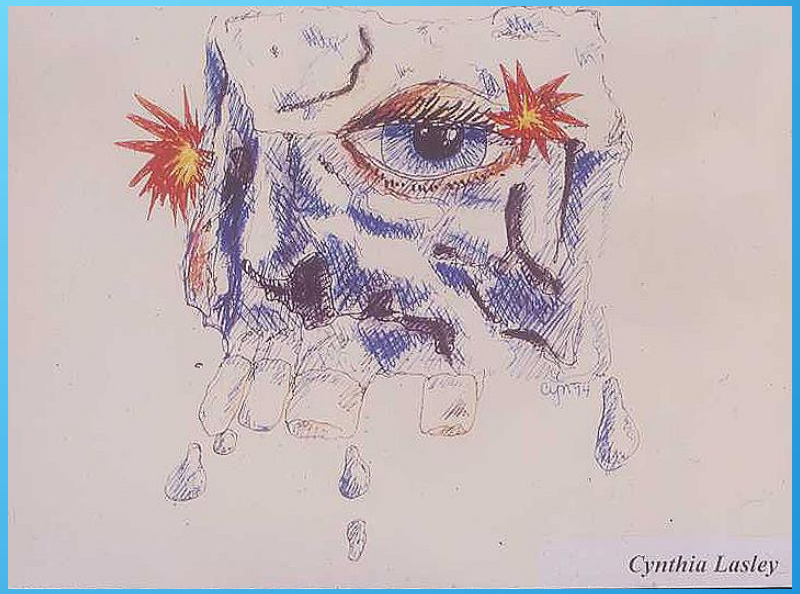


Immediate operative complications

- Death – up to 0.5% in MVD
- Hypotensive changes, arrythmias
- Heamorrhage – CVA
- Meningitis
- Headaches
- Deafness
- Herpes
- Local trigeminal
  - Sensory includes loss of corneal reflex
  - Deaffrentation pain – pain in a numb area
  - Motor
- Outside trigeminal nerve
  - 8th nerve
  - 6th and 4th nerve – diplopia
  - 7th nerve

Complications after surgery

- Local trigeminal
  - Sensory includes loss of corneal reflex
  - Deaffrentation pain – pain in a numb area
  - Motor
  - Outside trigeminal nerve
  - 8th nerve
  - 7th nerve
  - 6th and 4th nerve – diplopia



If Patient is unable to have MVD…

- Gamma knife
  - Sheffield ? 6 UK wide

Classification of Chronic orofacial pain

Trigeminal chronic pain

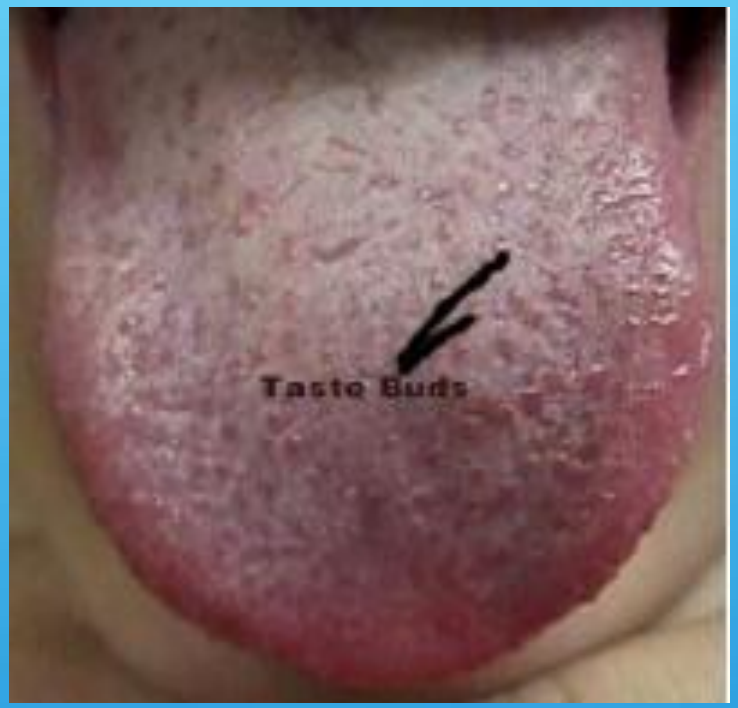
Neurovascular	Neuropathic	Idiopathic
Tension HA	Trigeminal N	Burning Mouth S
Migraine	Typical / atypical	TMJ pain
Cluster HA	PHN	Persistent idiopathic
Giant cell arteritis	Glosspharyngeal N	(ATFP / ATO)
SUNCT	Post surgical N	
	Lingual inferior alveolar nerve injuries	

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 <u>at least</u> 4-6 months.*

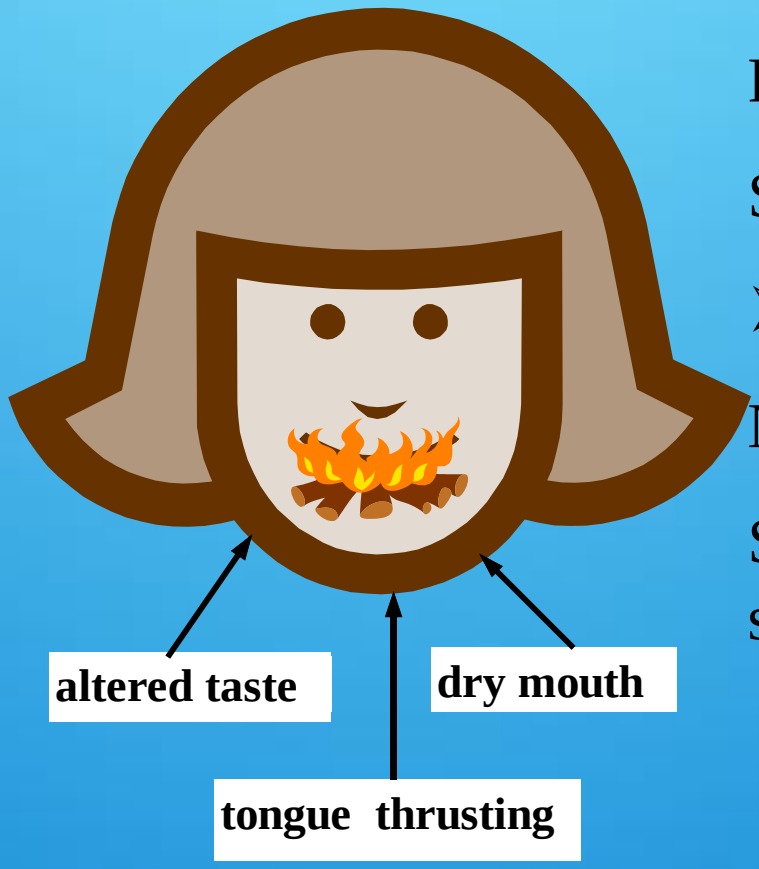
Prevalence: BMS

- 1-15% Tammiala-Salomen et al 1993
- 5.3% - Locker & Grushka 1987,1988
- 0.7% - Lipton et al 1993
- 2.6% - Basker et al 1978
- 10.3% - Jaafar et al 1989
- 1.7% - Richards & Scourfield 1996


Taste Buds

Burning Mouth Syndrome

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



Features

Spontaneous onset

➢4month duration

Normal appearance

Supertasters/taste sensitivity

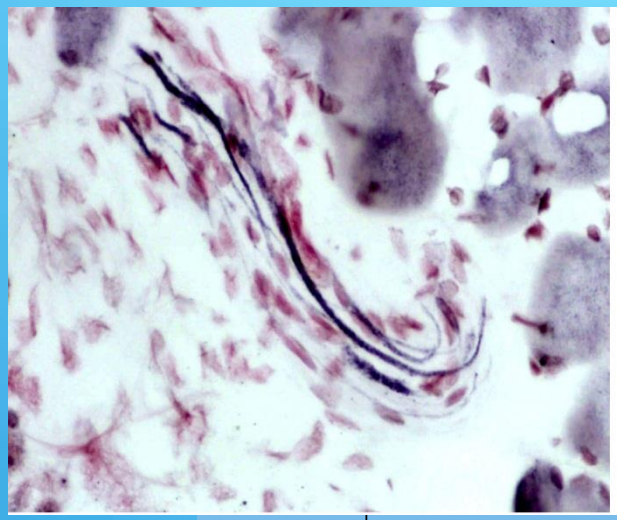
BMS causes

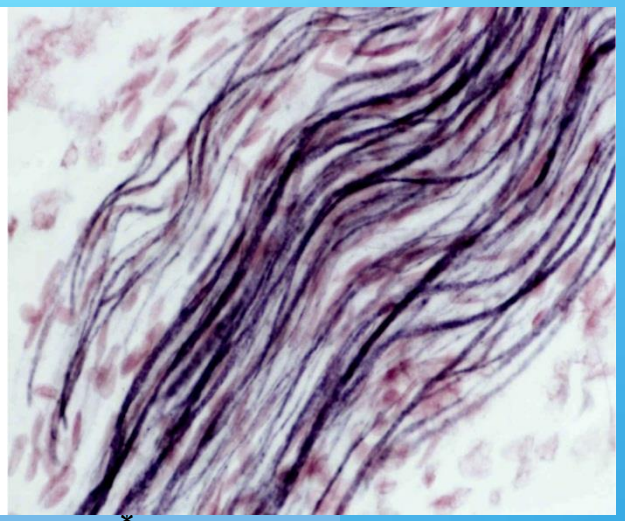
- Menopausal
- Supertasters
- Deficiency in Haematinics
- Psychometric - increased HADS scores
- Diabetes
- Neuropathy ??

NGF-IR

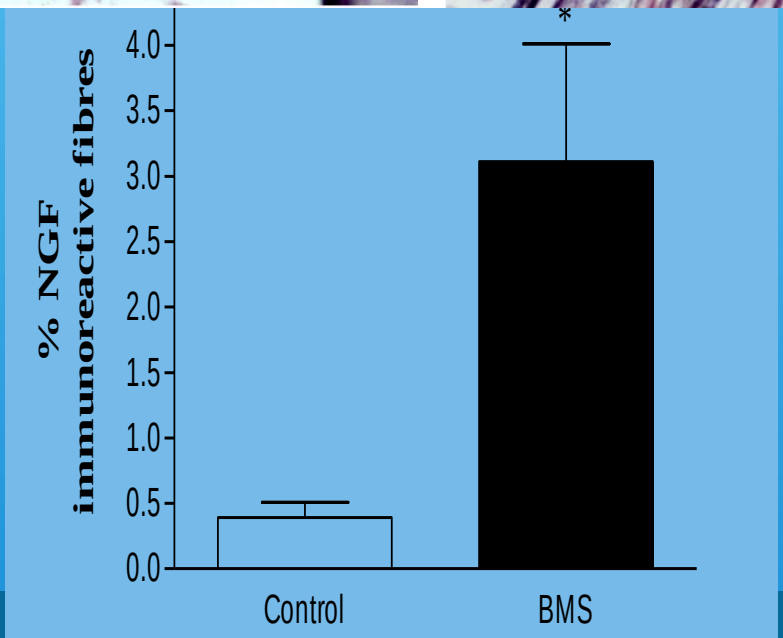
Control

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.

Management of BMS

- **Systematic Review** and data in Clinical Evidence
- Cognitive behaviour therapy may be beneficial
- Reassurance
- Notriptyline first line but limited evidence for use of antidepressants
- ? Future neuropathic pain blocking agents

Chronic idiopathic facial pain (atypical facial pain AFP)

- Character
  - Intense -Nagging, dull, throbbing, sharp, aching
- Severity
  - Varies, mild to severe though patient can often sleep and function normally
- Site, radiation
  - no anatomical area
- Duration, periodicity
  - Constant >6 months

Management of AFP /AO

- Counselling and reassurance
  - CBT
- Medical
  - Antidepresants
    - Tricyclic antidepressants
      - Amitryptiline
      - Nortryptiline 10mg,20mg,30mg,40mg each week. Maintain on 40mg nocte for 6 weeks before review
  - Anticonvulsants
    - Oxcarbazipine
    - Carbamazepine
    - Gabapentin
    - Pregabalin
- Topical local analgesia
- Capsaicin

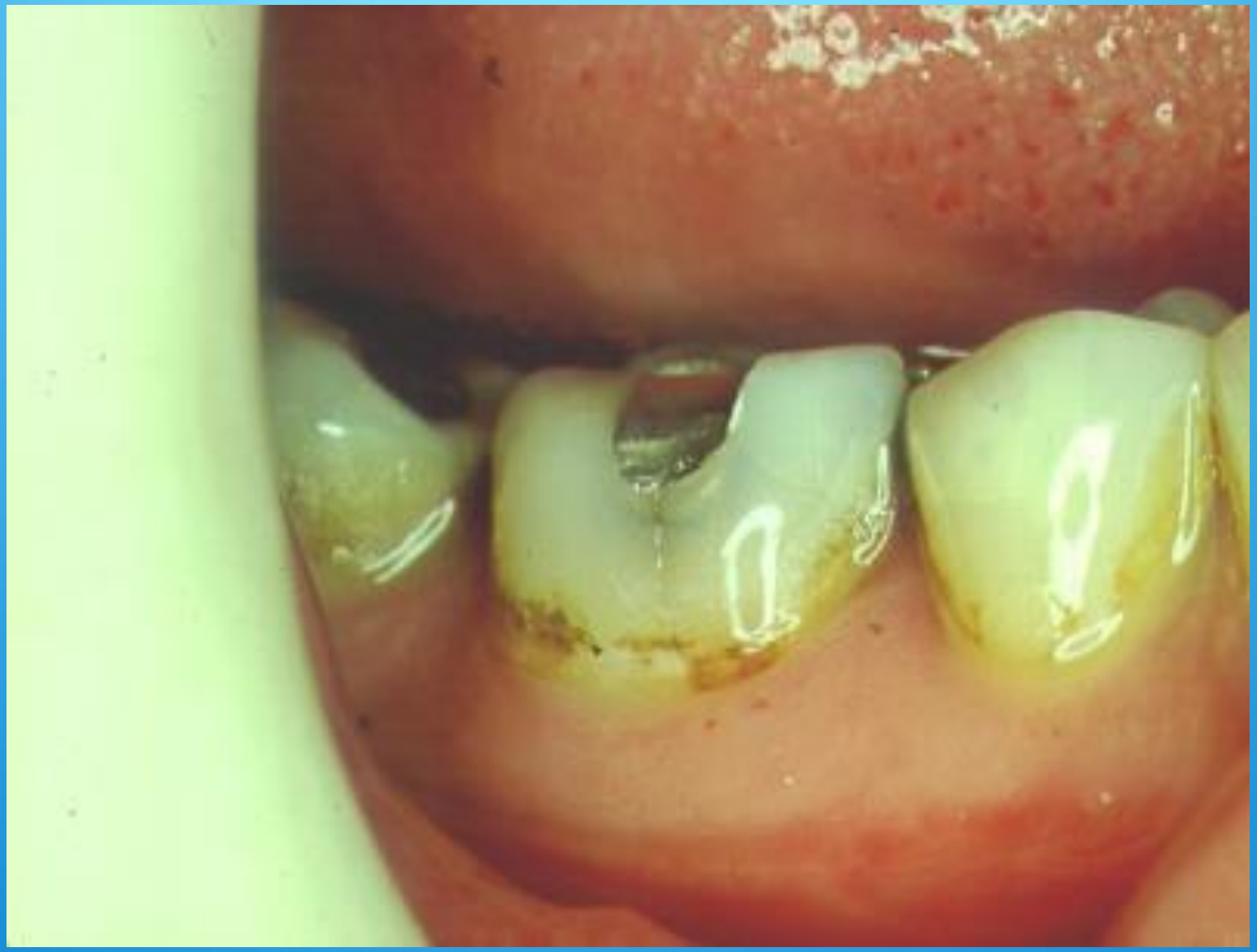
Chronic Idiopathic Facial Pain

- Provoking factors
  - Chewing, stress, opening mouth, tiredness
- Relieving factors
  - Rest, relaxation
- Associated factors
  - Pain in other areas, personality changes, life events, stress

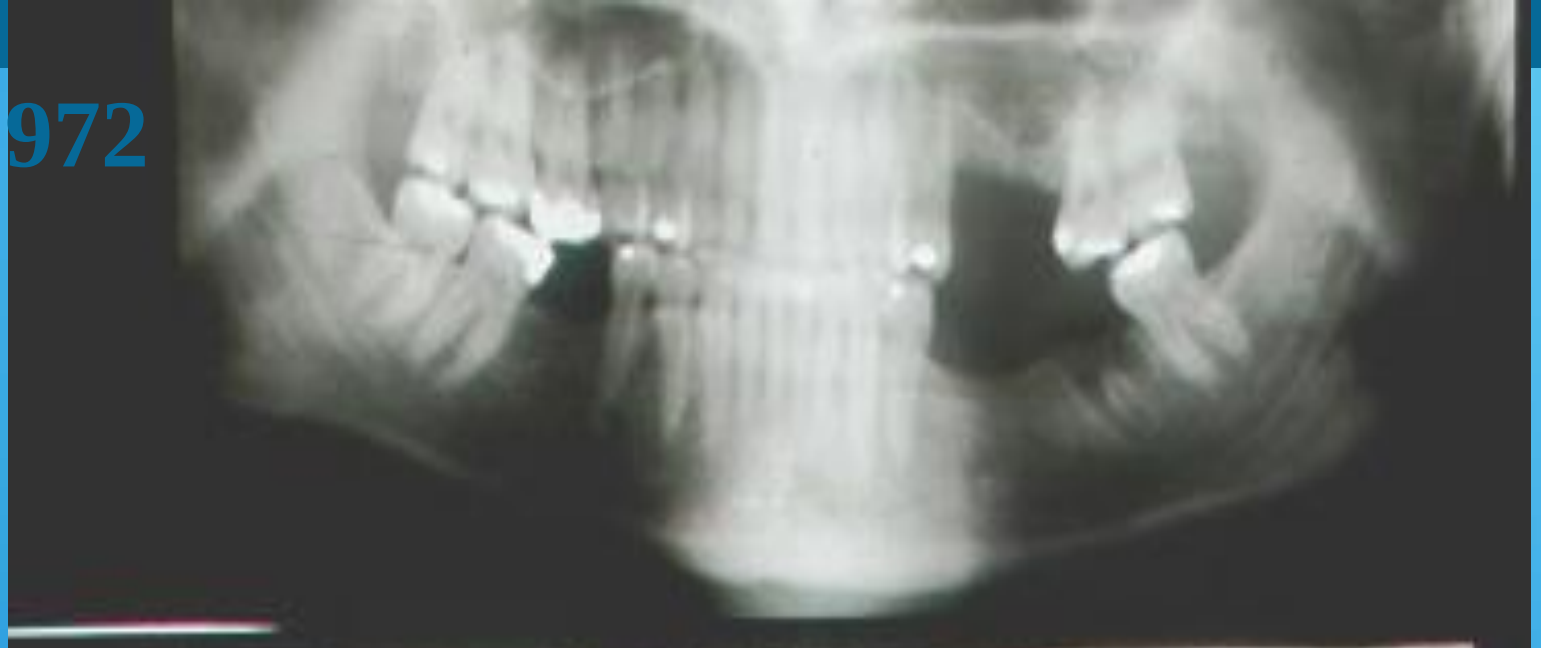
Atypical Odontalgia (Dental Allodynia)

- persistent dental pain
- hypersensitivity to all stimuli
- may migrate from tooth to tooth
- no detectable pathology

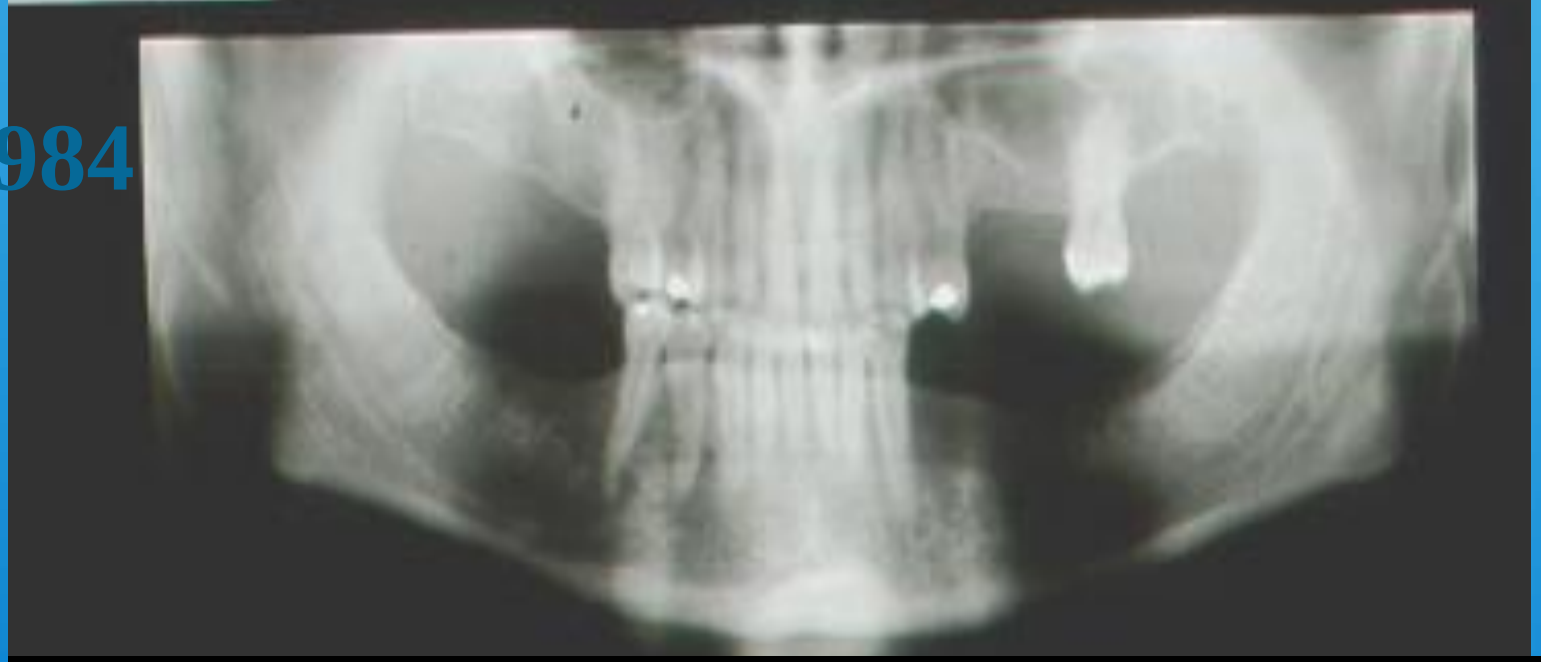
i.e not a split tooth



1972



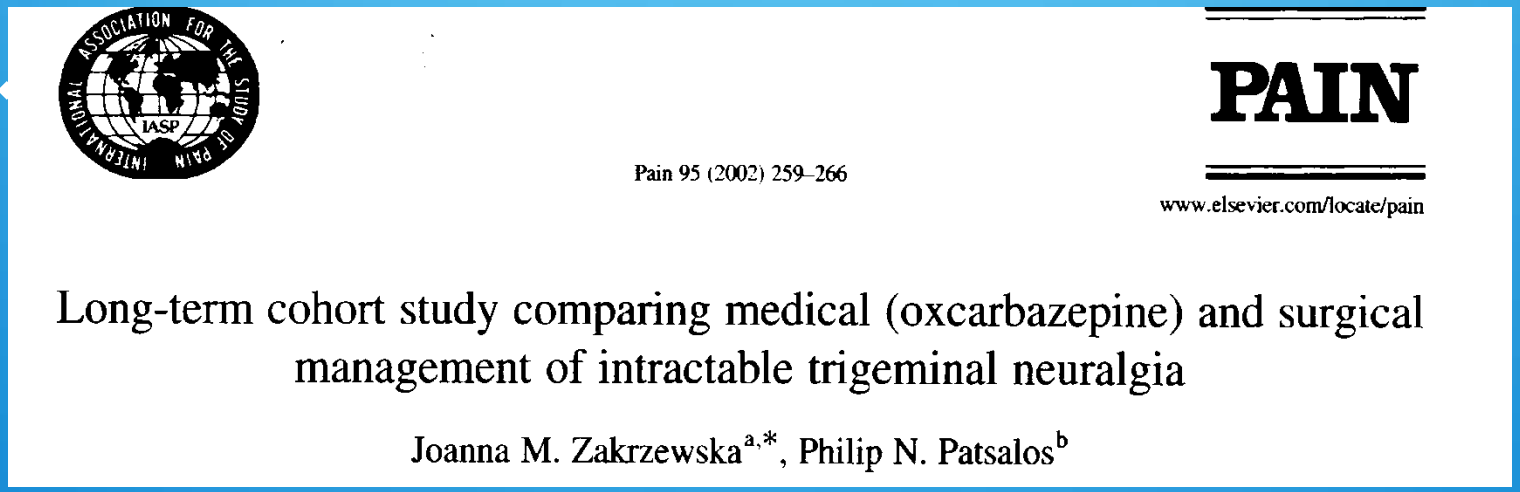
1984



Natural history of atypical odontalgia

Prognosis

- Chronic idiopathic facial pain – after one year 38% of patients pain free but 39% taking drugs to prevent relapse
- Feinmann and Harris 1984



Pain 95 (2002) 259–266

PAIN

www.elsevier.com/locate/pain

Long-term cohort study comparing medical (oxcarbazepine) and surgical management of intractable trigeminal neuralgia

Joanna M. Zakrzewska[a,*], Philip N. Patsalos[b]

12/15 required surgery to control their pain

TMD Natural History

- TMJ –less than 20% will continue to have continuous or increased pain
- one study showed that 3 years on only 5% still had TMJ pain
-
- Trigeminal neuralgia frequency of pain attacks increased with time

TMD

- Biopsychosocial
- Patient information
- BRA
- Cognitive behaviour therapy
- Antidepressants
  - Tricyclics- nortriptyline
  - SSRI – fluoxetine

TMJ Cochrane reviews

- Koh H Robinson PG Occlusal adjustment for treating and preventing temporomandibular joint disorders. J Evid Based Dent Pract. 2006.
- Al-Ani MZ Stabilisation splint therapy for temporomandibular pain dysfunction syndrome. Evid Based Dent. 2004;5(3):65-6.
- Koh H, Robinson PG Occlusal adjustment for treating and preventing temporomandibular joint disorders. J Oral Rehabil. 2004 Apr;31(4):287-92
- Bessa-Nogueira RV, Vasconcelos BC, Niederman R The methodological quality of systematic reviews comparing temporomandibular joint disorder surgical and non-surgical treatment. BMC Oral Health. 2008 Sep 26;8:27

- NO EVIDENCE !

- Non pharmacological methods
- Psychological
- Interpersonal strategies
  - Communication
    - reassurance
    - sympathy
    - understanding
  - Caring
  - Comfort
  - Consideration
  - Clinical Competence

Psychological factors in pain

- 20-50% of patients respond to Placebo!
- Increased anxiety / neuroticism / psychiatric morbidity
  - All predictive of persistent pain post operatively
- Cognitive behavioural therapy
- decreases pain in burns patients
- Increased use of OTC NSAIDs for headache with associated stress and poor physical fitness

Anxiolysis

- Non pharmacological
  - Interpersonal skills -reassurance
  - Hypnosis
  - Acupuncture
  - TENS
- Pharmacological anti-anxiety treatments
  - Single drug sedation (conscious)
  - Multiple drug sedation (deep)
  - Anaesthesia

Alternative analgesic therapies

- Homeopathic
  - Arnica reduces bruising and swelling
- Hypnotherapy
  - self hypnosis
  - induced hypnosis
- Counselling
  - Chronic pain patients may need counselling to improve their coping strategies
- CBT
- Biofeedback
  - training in changing function to reduce pain
- Tens shown to reduce the discomfort of ID blocks

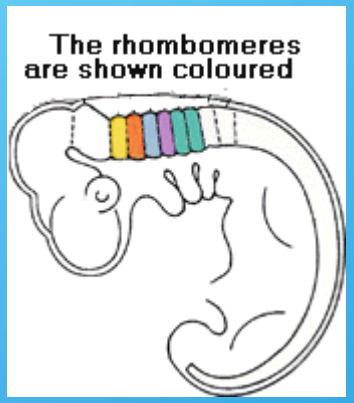
Management – Alternative

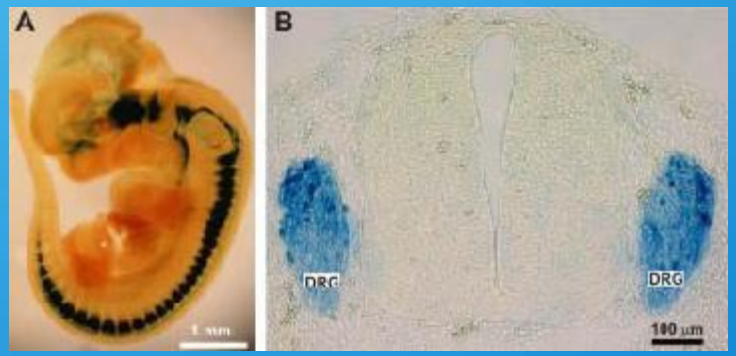
Self empowerment
Counselling

- Laughter
- Distraction
- Stress management – relaxation
- Exercise
- Social support
- Hypnosis
- Acupuncture
- Aromatherapy
- Pets
- Hobbies

The future

- Diagnose and Measure pain with fMRI
- Neural crest stem cells
  - Nerves
  - Immune cells





http://www.update-software.com/cochrane/

- **Anticonvulsant drugs for acute and chronic pain Wiffen et al**
- **Interventions for the treatment of burning mouth syndrome Zakrzewska JM et al**
- **Management of TMD with splints, injections**

Medical Management

- Wiffen et al Systematic review of anticonvulsants in neuropathic pain Cochrane Library
- Sindrup and Jensen Systematic review of drugs used in neuropathic pain Pain: 1999;389-400
- Zakrzewska JM , Lopez B Trigeminal Neuralgia Clinical Evidence 2003

Medical Management of facial pain

Evidence:

Cochrane library

http://www.update-software.com/cochrane/

Anticonvulsant drugs for acute and chronic pain Wiffen et al

Interventions for the treatment of burning mouth syndrome Zakrzewska JM et al

Clinical Evidence burning mouth syndrome and trigeminal neuralgia

VOLUME 14

PAIN RESEARCH AND CLINICAL MANAGEMENT

Assessment and Management of Orofacial Pain

Edited by J.M. Zakrzewska and S.D. Harrison

ELSEVIER

Migraine MIPCA 2002

- **Impact-based recognition of migraine**
- How do headaches interfere with your life?
- How frequently do you experience headaches of any type?
- Has there been any change in your headache pattern
  - over the last 6 months?
- How often and how effectively do you use medication
  - to treat headaches

- **Acute treatment strategy**
- Provide patient education and instruction
- Tailor intervention to the patient's needs and select the best
  - therapy for each patient
- Treat as early as possible in the attack
- Abort migraine symptoms and disability within 2–4 hours

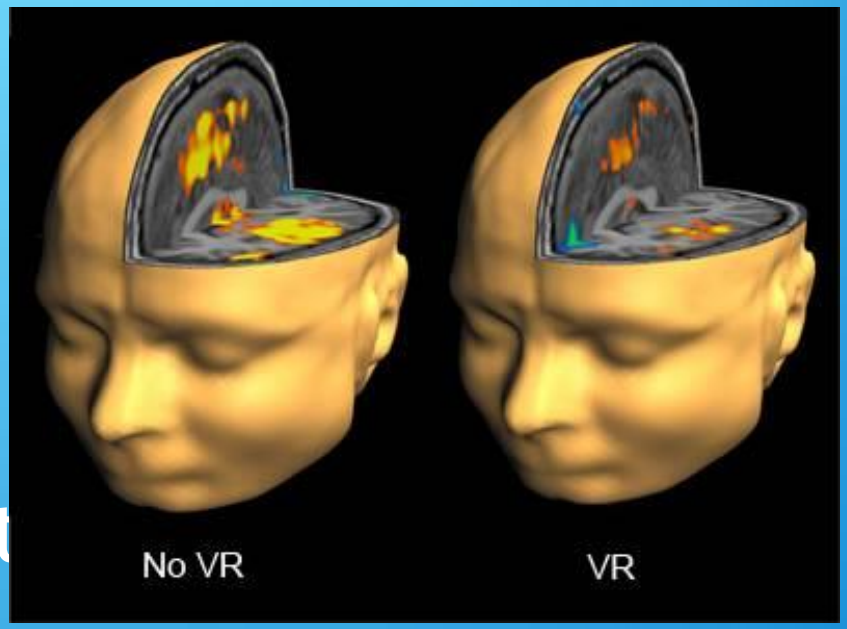
- **Preventative treatment strategy**
- Address patient expectations and compliance by
  - providing patient education and instruction
- Develop a formal management plan
- Use headache diaries
- Reduce attack frequency, duration, severity and disability
- Prevent the development of CDH
- **Choice of acute treatments**
- Mild headache: triptans, isometheptene, NSAIDs,
  - OTC combination analgesics
- Moderate to severe headaches: triptans or NSAIDS or
  - OTC combination analgesics if previously successful
- **Choice of preventative medications**
- Beta-adrenergic blocking agents
- Tricyclic antidepressants

DPF

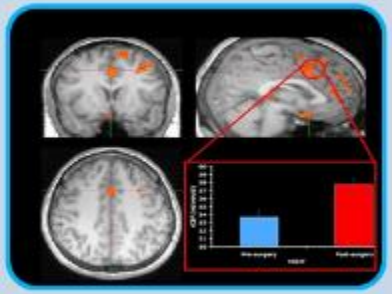
- Aspirin dispersable 300mg (1g)
- Ibuprofen tabs 200mg
  - Propionic acid derivative
- Iboprofen oral suspension 100mg/5ml
- Diflunisal tabs 250mg
  - Difluorophenyl derivative (Inc dry socket)
- Paracetamol tab 500mg
  - Acetaminophen – analine derivative
- Paracetamol sol tab 500mg
- Paracetamol oral susp 250mg/5ml
- Dyhydrocodeine tabs 30mg
- Pethidine tabs 50mg
  - Synthetic opioid

Management will depend on

- **The future.....**
- Prevention of chron
- Earlier recognition
- Tailored individual t



Peripheral receptors

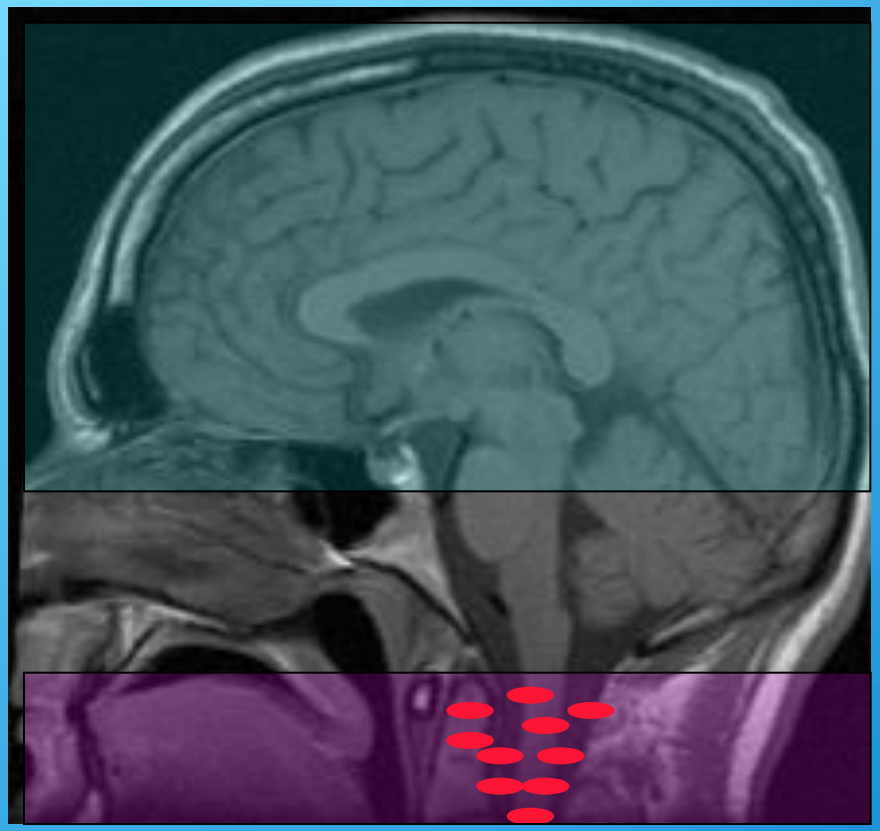


Central pain pathway

Genetics

Arterial spin labeling (cASL)

IMAGE ACQUISITION

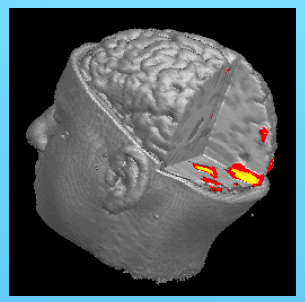


MAGNETISATION OF BLOOD

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

Pre-surgical visits

Ψ assessment & screening



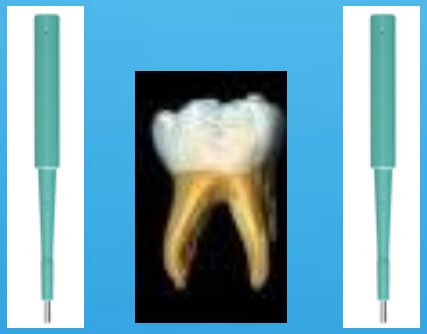
cASL assessment

post-scan RNA

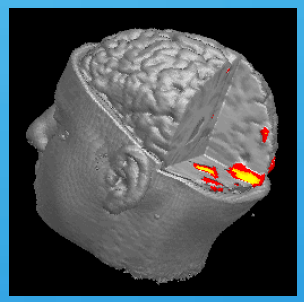
Surgical visits

Ψ assessment & screening

pre-surgery RNA



wisdom tooth extraction & mucosa



cASL assessment

post-scan/surgery RNA

the brain in man after third molar surgery

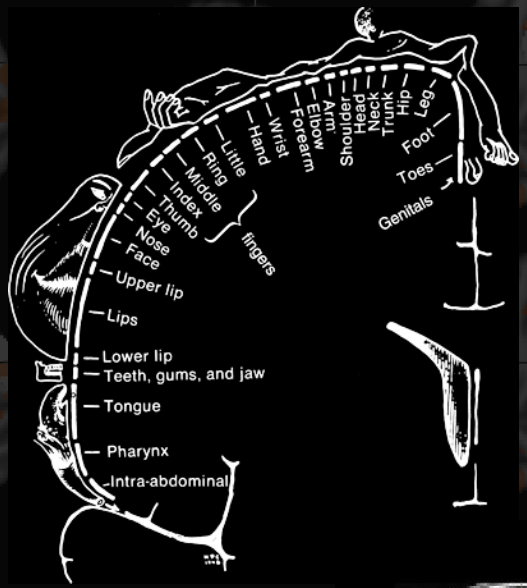
ACC

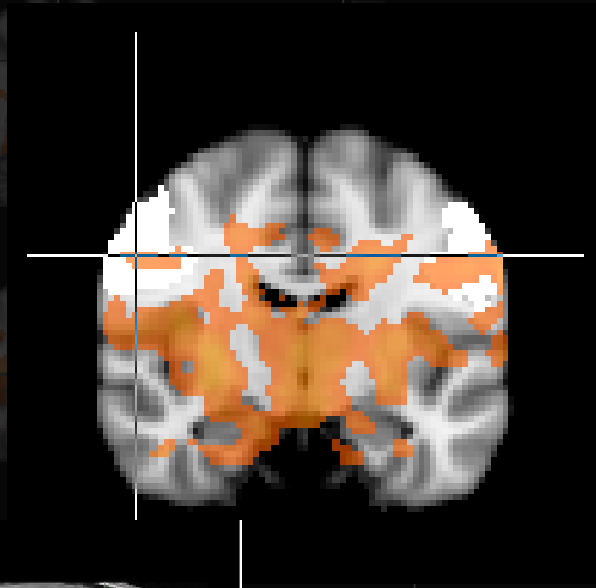
PCC

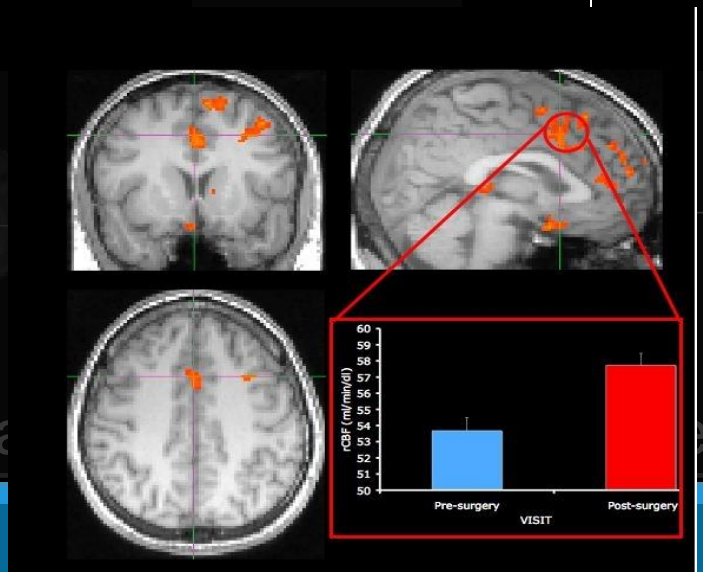
S1

S2

THAL

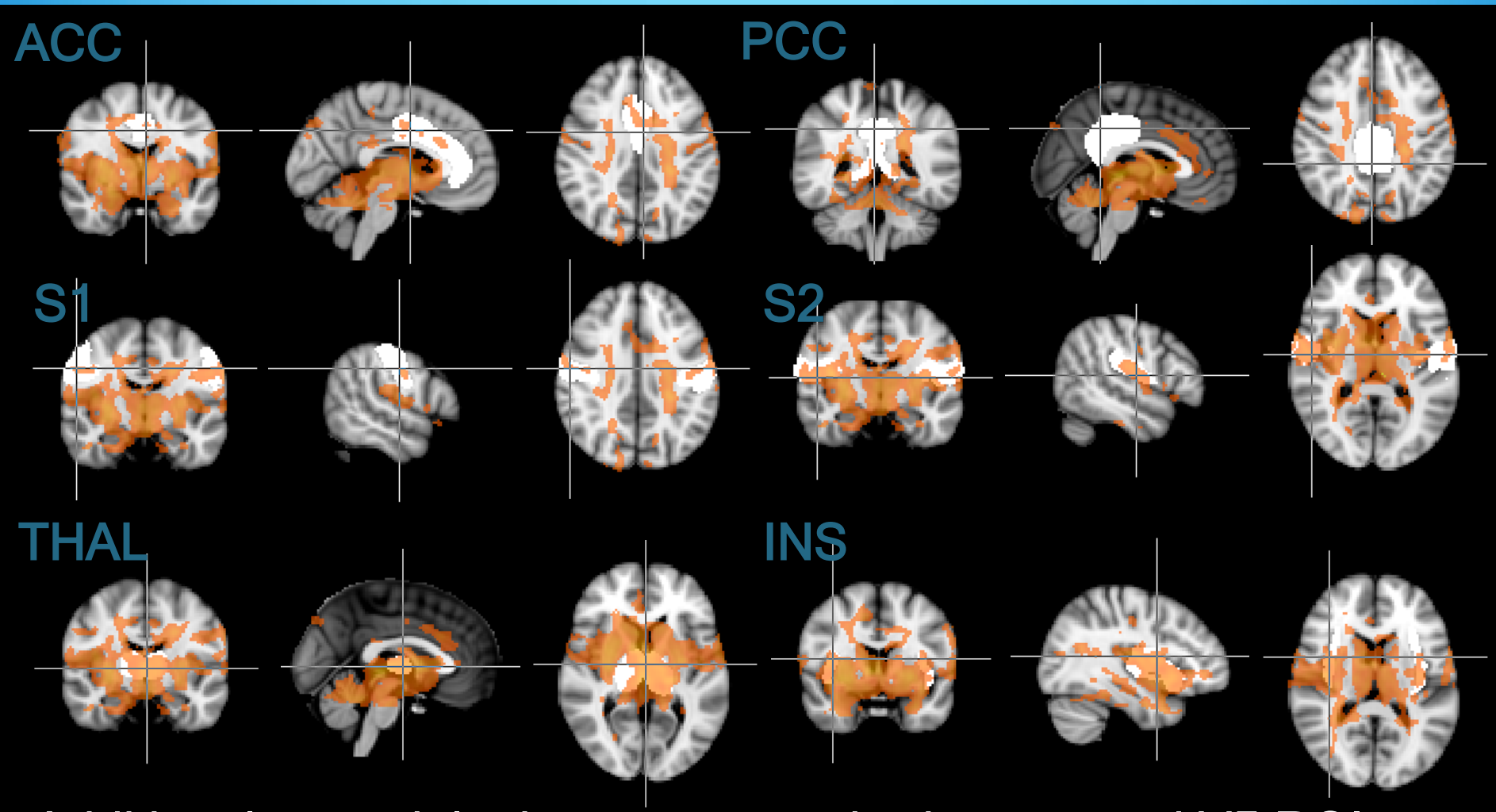






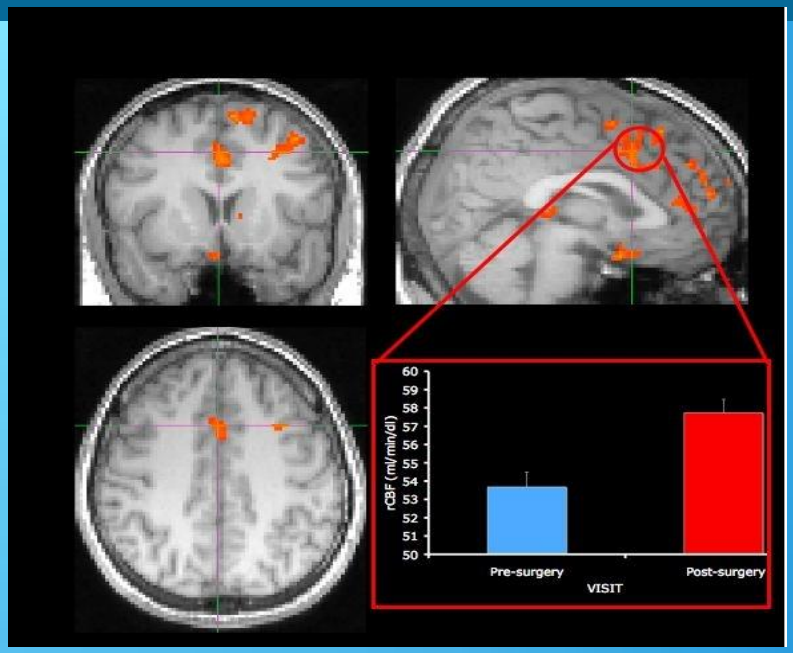
•Additional amygdala em, and V5 ROIs

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



- Additional amygdala, hippocampus, brainstem, and V5 ROIs

Results



Significant increases in post surgical rCBF observed in;

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

  Hemisphere (left or right)

Genetics

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

Post surgical pain
Gene expression & VAS score relationships

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