Orofacial pain: what’s new?

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

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

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

❖ **Institute of medicine USA 2011 report on pain**
Chronic pain: Consequences UK

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

What is pain?

• Mechanisms

Orofacial pain
Understanding pain

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

- Mainonides (1138-1204): Galen’s art heals only the body but Abou Amrans heals the body and soul.

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

- Nociception
- Sensation
- Behaviour
- Suffering
What is pain?

<table>
<thead>
<tr>
<th>Subjective sensation</th>
<th>• with physical and psychological effects</th>
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<tbody>
<tr>
<td>Individual response</td>
<td>• dependant upon</td>
</tr>
<tr>
<td></td>
<td>• age / gender / experience / personality / anxiety</td>
</tr>
<tr>
<td></td>
<td>• settings / trust in clinician / fatigue</td>
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<tr>
<td>Organic and or psychological cause</td>
<td></td>
</tr>
<tr>
<td>Measure</td>
<td>• Black line 10cm long?</td>
</tr>
<tr>
<td></td>
<td>• questionnaires to assess disability</td>
</tr>
<tr>
<td></td>
<td>• physical / mental</td>
</tr>
</tbody>
</table>
HOW DO WE FEEL THE "OUCH"?
Pain Process

Bio psycho social Model

Nociception

Sensation

Behaviour

Suffering

Social / cultural
Age, gender, race, peer support, familial expectation

Cognitive / conceptual
Memories past experience, secondary gain, threat perception

Emotional / psychological
Depression, anxiety, stress, fear, anger
NOCICEPTION-

Inflammation
action potential
neural propagation of pain
ends sensory cortex
Nociception

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

Peripheral events
Injury chemical, physical, thermal, radiation and chemical

Skin

Inflammatory soup

Cell membrane phospholipids

Arachidonic acid

Oxygenderation

Phospholipase A2

Cox-1 inhibitor
Aspirin / Ibuprofen

Cox-1

PGs

Gastric Mucosal Barrier
Renal function
Thromboxane A
Platelet aggregation
Vasoconstriction

Cyclooxygenase

Cox-2 inhibitors

Leukotrienes

LTB4

5-LO inhibitors

Lipid Oxidation
5-LO peroxygenase

Cox-2

Prostaglandins

Pain, inflammation
Fever
Prostacyclin
Platelet inhibition
Vasodilatation

Cytochines
TNF alpha
IL beta
TNF antagonists

Inflammation
Broncho constriction
Airway obstruction
Cell infiltration
Anaphylactoid synds
Specific pain receptors

- Transmitters
  - ↓ NGF, ↓ SP, ↓ CGRP

- Receptors
  - ↓ TRPV1, ↓ P2X3

- Ion Channels
  - Na, Ca, K

- Anatomy
  - degeneration

- ↑ spontaneous activity
Control Pain

% NGF immunoreactive fibres

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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 histamine
- Bradykinin
- Nerve growth factor NGF
Nociception central events
CNS and PNS

Receptor

Primary sensory nerve
- A Delta and C fibres

Secondary sensory nerve
- Lamina I DRG

Tertiary sensory nerve
- Specific areas of the brain
  - Thalamus
  - Anterior cingulate cortex
  - S1 / S2
  - Insula
  - Brainstem
Noxious stimulus
What events unfold in the sensory system?

<table>
<thead>
<tr>
<th>Neurophysiological</th>
<th>Patient</th>
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</thead>
<tbody>
<tr>
<td>• Peripheral nervous system PNS</td>
<td>• Clinical symptoms</td>
</tr>
<tr>
<td>• Inflammation</td>
<td>• Psychological factors</td>
</tr>
<tr>
<td>• Receptors</td>
<td>• Environmental factors</td>
</tr>
<tr>
<td>• Axons (primary / secondary / tertiary [cortex])</td>
<td>• Reaction is Emotional and Physical</td>
</tr>
<tr>
<td>• neurotransmission</td>
<td></td>
</tr>
<tr>
<td>• Central nervous system CNS</td>
<td></td>
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<tr>
<td>• Pain pathways</td>
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</table>

[Image of neural pathways and brain regions]
Neuro inflammation
Cellular events

Astrocytes

Somatosensory Cortex I and II

Microglia

- (Macrophages invading the CNS)

Schwann cell

Macrophages

- Bradykinin
- ILB
- Nerve growth factor (NGF)

Mast cell

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

Lymphocytes/Neutrophils

- ILB
- Endorphins acting on -CRK, GABA α, SSTR2α, M3

Neuroinflammatory

- Central centres
- Spinal cord
  - Receptor
    - CCR2
    - CCR1
    - CCR3
    - CX3CR1
  - Ligands
    - CCL2 (MCP-1)
    - CCL5 (MIP-1α)
    - CX3CL1 Fractalkine
- Dorsal root ganglion
  - Receptors
    - CX3CR1
    - CCR5
    - CXCR4
  - Ligands
    - CCL2 (MCP-1)
    - CCL21 (SLC)
    - CX3CL1 Fractalkine
- Peripheral nerve
  - Receptors
    - Heat shock TRPV1
    - TTXR Nav
    - SHT
    - M1
    - IL 1 and 8
    - TRA
  - Ligands
    - P2X3
    - A5
    - ASIC
    - glutamate
    - CCL2 (MCP-1)
    - CCL5 (MIP-1α)
    - CX3CL1 Fractalkine

Tissue damage leads to release of:

ATP
Adrenaline
Protons H+
Activating PNS neurons directly
SENSATION
Central neuroanatomy

- Pain related areas
  - Spinal cord C1–S5
    - C1–8/T1–12/L1–5/S1–5
    - distal root ganglion
    - Ventral horn = motor
    - Dorsal horn = sensory

- Specific areas of the brain
  - Brainstem
    - Cranial nerve
    - Thalamus
    - Hypothalamus
    - Cerebellum
  - Forebrain
    - Cortex–sensation
      - Anterior cingulate cortex
      - S1 and S2
    - Limbic system –memory
    - Basal ganglia–movement
- **OUT** Trigeminal Nerve root-V ganglion
- **Mesencephalic V nucleus** = proprioception
- **IN** Trigeminal (V) Lemniscus-to VPM N thalamus - S1 and S2
- **Motor V nucleus** = masticatory muscles
- **Pontine V nucleus** = main sensory N touch
- **Spinal V nucleus** subdivided vertically-
  Oralis / interpolaris / caudalis (Pain+temperature)
OUT Trigeminal Nerve root-V ganglion

Mesencephalic V nucleus = proprioception

IN Trigeminal (V) Lemniscus-to VPM N thalamus - S1 and S2

Motor V nucleus = masticatory muscles

Pontine V nucleus= main sensory N touch

Spinal V nucleus subdivided vertically-
Oralis / interpolaris / caudalis (Pain+temperature)
Anatomy revisited Sensory cortex V

• Additional amygdala, hippocampus, brainstem, and V5 ROIs
Main effect of TME pain, right tooth, cluster corrected \( \alpha < 0.05 \)
Central pain activity

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

- History
- Stress
- Anxiety
- Culture
- Ethnicity
- Beliefs
- Age
- Environment
- Context
Affective emotional areas of Brain

- Sensory Regions: Primary Sensory Cortex, Thalamus, Posterior Insula
- Emotional/Affective: Anterior Cingulate, Posterior Cingulate, Orbitofrontal Cortex, Medial Prefrontal Cortex, Anterior Insula, Accumbens, Hippocampus, Thalamus, Amygdala, Caudate
- Cognitive/Integrative: Prefrontal Cortex, Temporal Lobe, Parietal Cortex

Pain Inputs into Sensory Regions: Emotional and Cognitive Regions

Images showing brain activity for Pain and Empathy.
Perception of pain
Perception of pain

‘I enjoy the pain’
David Beckham on tattoos

Opus Dei Priest ‘Pain is good’
Suffering

History
Stress
Anxiety
Culture
Ethnicity
Beliefs
Age
Environment
Context

Personality
Religion
Placebo
Anger
Catastrophising
Fear
Catastrophising

Anxiety stress and pain

Psychological factors driving pain


Alternative and holistic management of pain


Clinician understanding and empathetic Good treatment planning expectations
Managing patients' expectations of surgical related pain is effective in pain relief!

TYPES OF PAIN
Types of acute pain

- Nociceptive
- Inflammatory
Pain: Acute

‘Healthy pain’ due to inflammation

Infection / autoimmune / trauma

Thermal / mechanical / chemica
Why does the acute pain patient present?

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

Nociceptor

Low-Threshold Mechanocceptor

Pain

Touch

Nociceptor

Low-Threshold Mechanocceptor

Pain

Touch
Chronic pain

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

B Inflammatory pain

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

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

Unhealthy / Neuropathic pain lasting > 3 months
Back pain 47.5%
Head ache 45.2%
Joints 41.7%

Disease of the neuromatrix
Why does pain become chronic?

Persistent acute stimulus becoming chronic
- Increased sensitivity of CNS to peripheral stimulus

Neuroplasticity
- Interaction between PNS and CNS results permanent changes in system

Memory of pain
- Somatosensory cortex changes

Genetic predisposition
Peripheral and central interaction: The ‘neuromatrix’

Functional measures

A. Brain areas functionally related to pain processing.

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

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

Ethan Kross et al., Proceedings National Academy of Science USA. Social rejection shares somatosensory representations with physical pain
Structural Brain Imaging: A Window into Chronic Pain.
Arne May. The Neuroscientist 17(2) 209-220:2011

- Neuroplasticity
- Cortical reorganisation
- Gray matter changes
- Central sensitisation
- Maladaptive plasticity
- Downward facilitation
- Downward inhibition
(Placebo effect)
Structural Brain Changes: Cause or Consequence of Chronic Pain?

- Numerous modulatory mechanisms have been postulated and altogether addressed as “neuronal plasticity” (Woolf and Salter 2000), and structural changes of the brain need to be added to this list (May 2008).

- Gray matter changes: The key message of all three studies is that the main difference in the brain structure between pain patients and controls may recede when the pain is cured.

- The impact of pain killers and other medications on morphometric findings is simply not known.

- Chronic nociceptive input leads to intra cortical remodelling.

- We need to improve our understanding of experience-dependent changes in cortical plasticity as this will have vast clinical implications for the treatment of chronic pain.
Loss gray matter

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


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

- Reduction gray + white matter TMD


- Gray matter reduction in TN

Cortical reorganisation

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

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

- Facilitation
- Augmentation
- Potentiation
- Amplification

=hypersensitivity

Alban Latremoliere & Clifford J. Woolf Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity.
Maladaptive plasticity, memory for pain


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

Genetics and pain
Six children from three related Pakistani families feel no physical pain.

Although capable of feeling other sensations like warm and cold, they have a lack of pain perception.

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 Nav1.7 sodium channel deficiency.
Genetics of pain

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

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

<table>
<thead>
<tr>
<th>Improved diagnostics and patient care</th>
<th>• (e.g. „customised“ medication) with side effect reduction, risk management</th>
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<tbody>
<tr>
<td>Cost of genetic analyses will decrease</td>
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<tr>
<td>More information on biological functions of genes and proteins</td>
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<tr>
<td>Increased interdisciplinary work</td>
<td>• (imaging genomics, proteomics, QST)</td>
</tr>
<tr>
<td></td>
<td>• Epigenetics will receive increased attention</td>
</tr>
<tr>
<td>Increasing numbers of papers on pain genetics</td>
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</table>
New conditions-novel research

- Neuropathic pain NePain
- CRPS
- BMS
- Acute pain V studies
Painful Posttraumatic Trigeminal Neuropathy: A Recently Recognized Entity

An unusual event recently occurred in the field of chronic orofacial pain. A new entity has been established through a few research papers and meetings of experts. Different specialists have known for some time that surgery and other traumatic events may injure the trigeminal nerve and provoke symptoms. Nerve damage may occur during Caldwell-Luc intervention, orthognathic mandibular advancement surgery, extrusion of root canal filling materials, implant surgery, and various traumatic events such as facial fractures and therapeutic radiation; third molar removal is the most frequent cause. Several branches of the mandibular or maxillary division of the trigeminal nerve could be involved, such as the infraorbital nerve, the superior alveolar nerves, and most frequently the lingual and inferior indicated that the 20 cases of PPTTN found among 245 cases of chronic orofacial pain tended to cluster. This was in line with a recent study performed on 328 patients with chronic orofacial pain that indicated that over 12% of the cases were PPTTN. These two studies pointed to a much larger prevalence than what was previously suspected, even if these samples were far from being representative of the general population since they came from tertiary care centers. The contribution of the different specialties to the incidence of PPTTN has been recently detailed.

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

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


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

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

Mechanism NePain

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

CRPS

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

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

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

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

Complex Regional Pain Syndrome Reflex Sympathetic Dystrophy

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

- Inflammatory nociceptive pain
  - *Dental Pain* Peripheral + genetics
  - *Post surgical pain* Genetics, Peripheral and central

- Neuropathic pain
  - *Post Traumatic Neuropathy* Genetics, Peripheral and central psychometrics
  - *Trigeminal autonomic cephalgias* Genetics, Peripheral and central
  - *Trigeminal neuralgia* Genetics, Peripheral and central
  - *Burning mouth* Genetics, Peripheral and central
Unravelling toothache

Immortalised cell line of odontoblastic +ve markers TRPA1, TRPV1 and TRPV4.

Microarray, RT-PCR, flow cytometry and Calcium imaging studies

Obi Egbuniwe PhD St
Prof Lucy Di Silvio
Dr Andy Grant

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

- Enamel
- Dentine
- Pulp
- Dentine pulp complex

Research
Nociceptors in dental pulp


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

Work with Prof Steve MacMahon & Dr Andy Grant
Burning Mouth Syndrome

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

Features
Spontaneous onset
4month duration
Normal appearance
Supertasters/taste sensitivity
Dr Kiran Beneng PhD St
Prof Praveen Anand
Dr Zehra Yilmaz

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

Dr Matt Howard

NF Bar charts of the mean ± SEM of epithelial nerve fibres per papilla in control and BMS tongue. * P <0.0001.
P =0.0006, Spearman r =0.55
Bar charts of the mean ± SEM of epithelial nerve fibres per papilla in control and BMS tongue. * P <0.0001.

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

Control  BMS

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

% NGF immunoreactive fibres

x40
TRPV1 fibres staining in control and in BMS x20.

Bar chart shows the mean ± SEM of % area of TRPV1 fibres in control (n=10) and BM (n=10) tongue. * P =0.0011
Correlation of TRPV1 fibre IR with VAS Pain score

P = 0.0006, Spearman r = 0.55
Immunohistochemical labelling of TRPA1 and TRPM8-positive rat tongue cells using Alexa Fluor® 488

Immunocytochemical labelling of collagen type I and dentin sialophosphoprotein-positive human odontoblast cells
Post surgical acute pain
Imaging post surgical pain

- TME most frequent model in acute pain trials (Moore et al., 2005)
- 30-80% of patients suffer moderate to severe
  - pain post-operatively

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

ψ assessment
nt & screening

RNA Ψ assessment & screening

cASL assessment

post-scan RNA

Surgical visits

ψ assessment
nt & surgery

pre-

wisdom tooth extraction & mucosa

cASL assessment
nt

post-

scan/surgery RNA
Arterial spin labeling (cASL)

- cASL can quantify cerebral blood flow (CBF) changes in active brain areas responding to pain.
- Examine ongoing TME pain to provide an objective measure of pain.
Measuring pain centre activity in the brain in man after third molar surgery

- Additional amygdala, hippocampus, brainstem, 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
  - Presurgery /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
Clinical, imaging and genetic characterisation of Cluster headaches

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

Trigeminal autonomic cephalgias
Cluster headaches
SUNCT and SUNA
Post traumatic neuropathy (lecture 3)
TRIGEMINAL NERVE FOUNDATION
Orofacial pain website

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

THANK YOU