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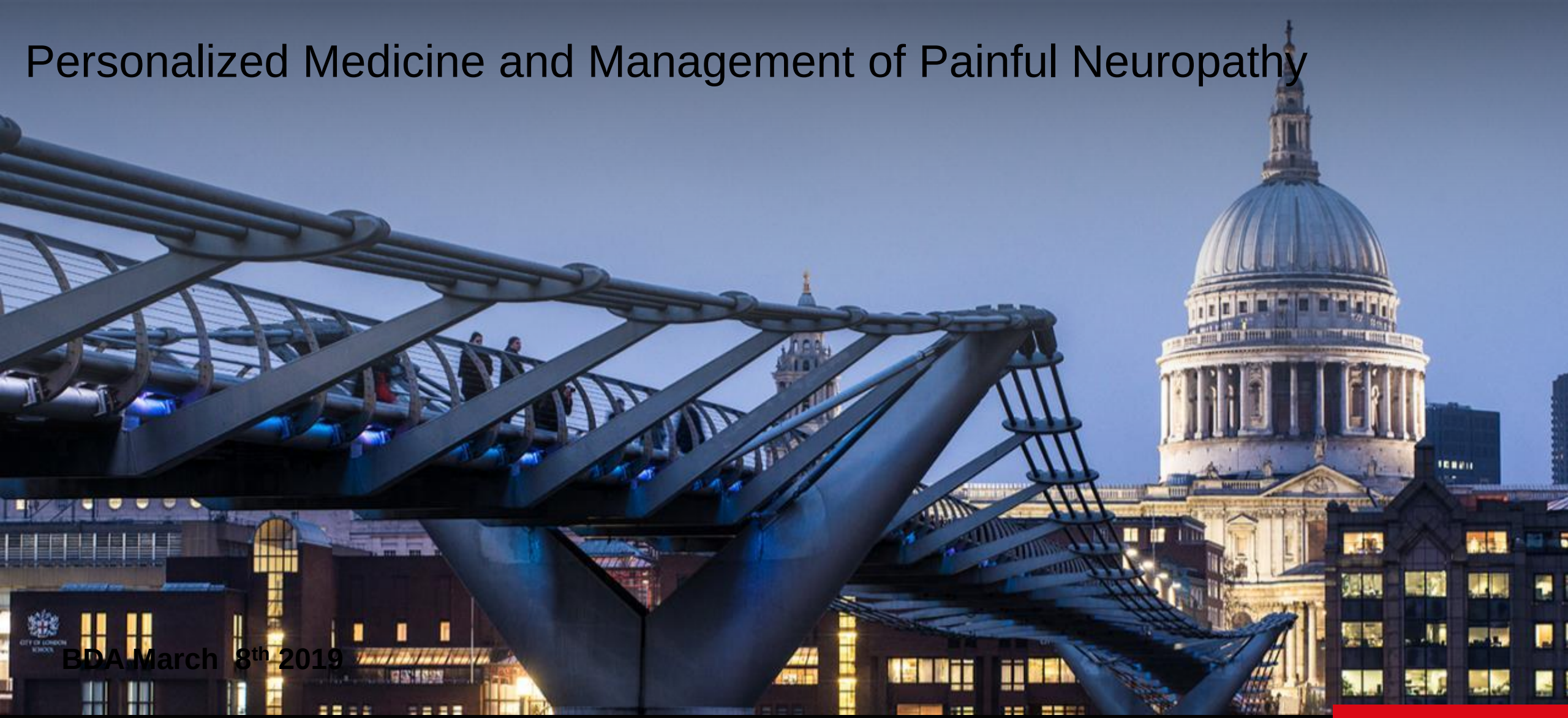
Personalized Medicine and Management of Painful Neuropathy



BDA March 8th 2019

Faculty of Dentistry, Oral & Craniofacial Science

Tara.renton@kcl.ac.uk
Professor Oral Surgery Kings College London Past President British Association of Oral Surgeons

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Aims & Objectives

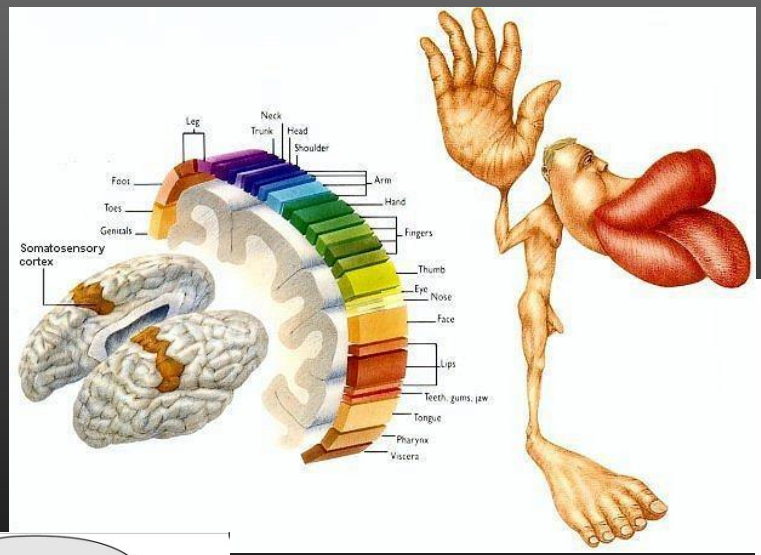
To enlighten the attendees of;

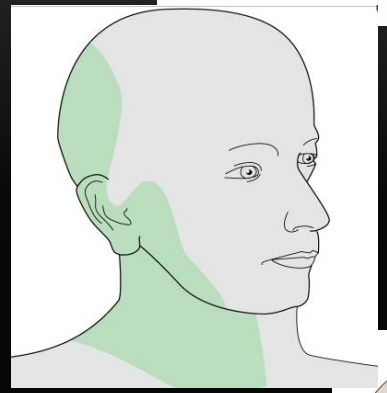
- Using a stratification approach to orofacial pain
- MRI arterial spin labelling identification of central pain pathways, connectivity and downward modulation in orofacial pain
- An update on the use novel interventions for orofacial pain including stimulation

Why is Trigeminal pain unique?

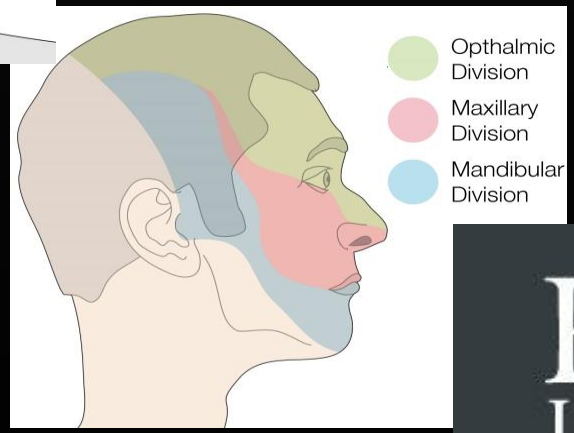
- Primordial brain - survival instincts
- Constant unavoidable activity
- C2,3 and vagal interaction (autonomic input)
- Underpins daily pleasure in health
  - Eating
  - Drinking
  - Speaking
  - Smiling
  - Sexual interaction
- **Bilateral cortical representation of pain**
- Thus any threat or actual harm to the V*th* nerve region comprises a massive threat to your very existence

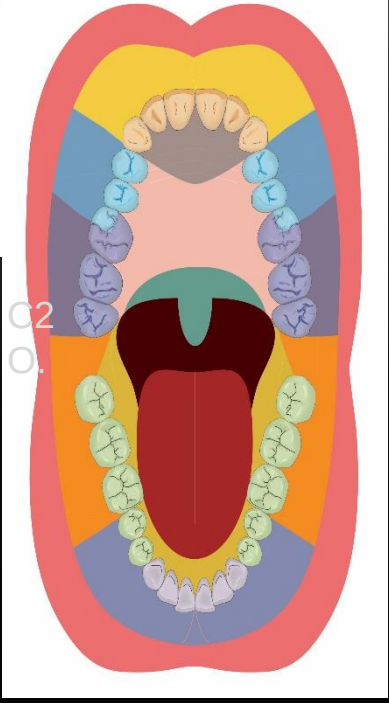
All patients are physiologically wired to run from the dentist!





The dermatomal distribution of C2 and C3 (Adapted from Foester O. The dermatomes in man [Schorstein Lecture, London, 1932]. Brain 1933;56:I-39.)





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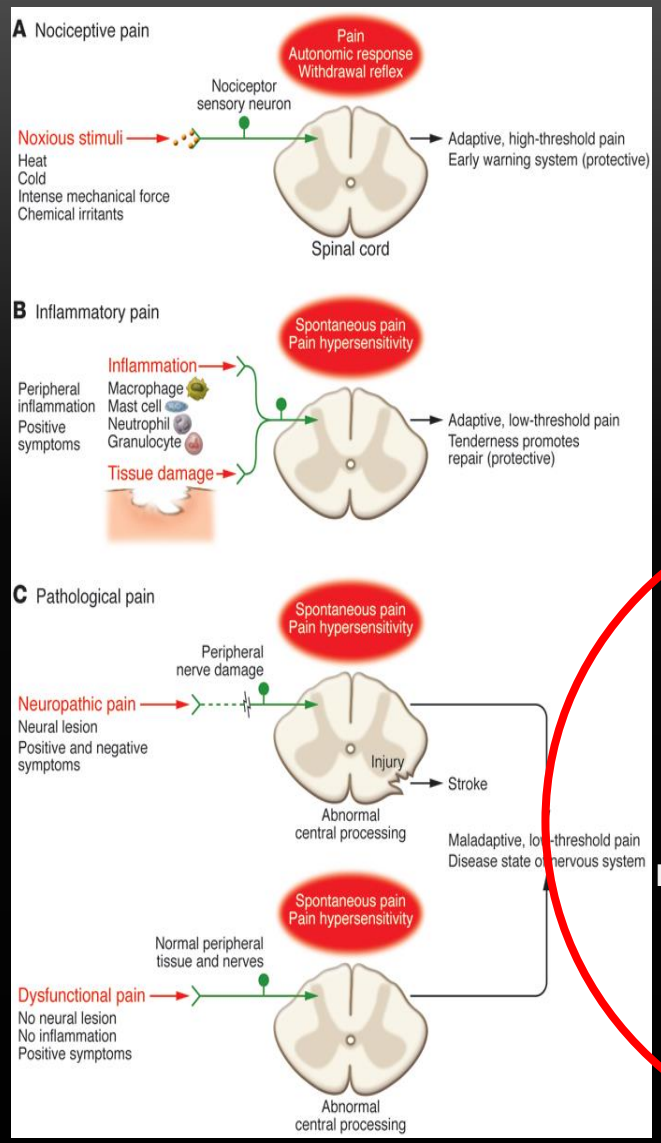
Definitions of pain



Healthy acute pain

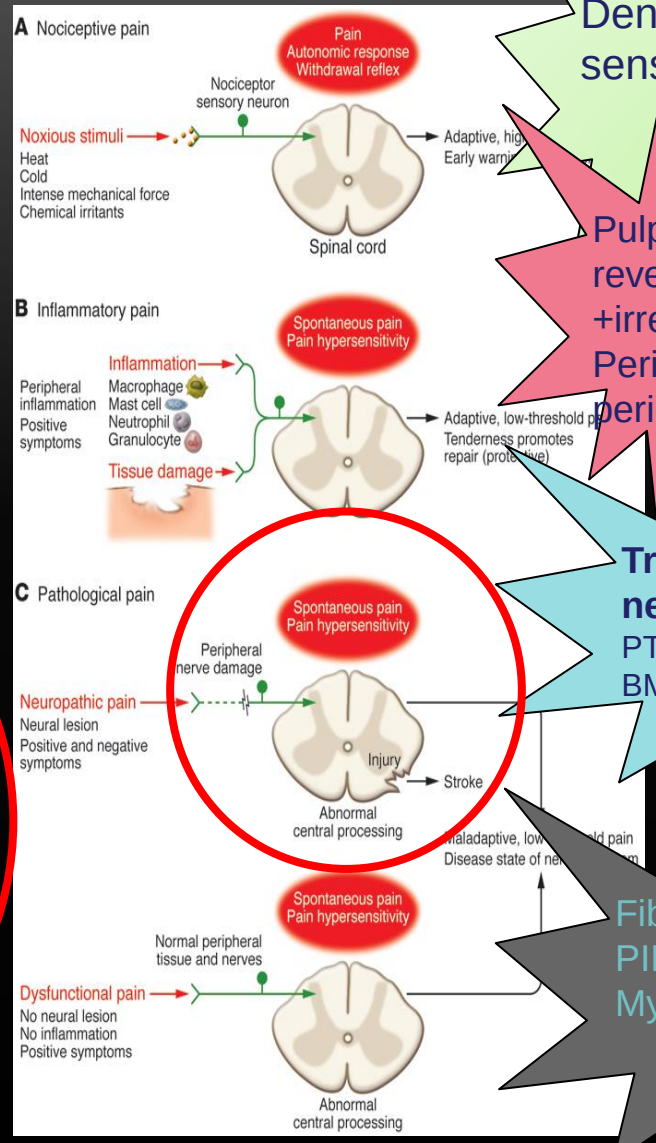
Nociceptive
healthy feeling pain 'pain'

Inflammatory pain
healthy short lived after insult

Chronic pain = disease of neuromatrix

<u>Neuropathic pain</u>
<u>Associated with nerve lesion</u>

Dysfunctional or centralised pain
Unknown cause



Dentine sensitivity

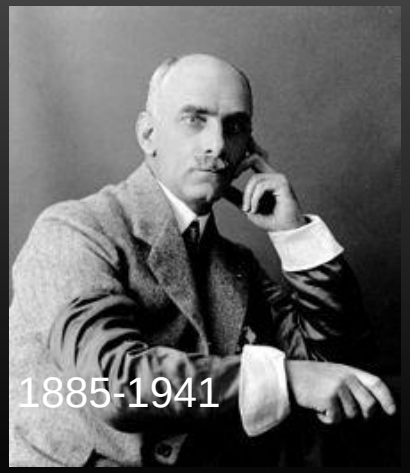
Pulpitis reversible +irreversible
Periapical periodontitis

Trigeminal neuropathic pain
PTN, CPSP, 2y TN, BMS, PDAP/ PHN

Fibromyalgia
PIFP
Myofacial TMD

Pain diagnosis

Thomas Lewis FRS



1885-1941

“Diagnosis is a system of more or less accurate guessing, in which the end point achieved is a name. These names assume the importance of specific entities, whereas they are for the most part no more than insecure and therefore temporary conceptions.”

BUT …..The same diagnosis on different patients requires different interventions and may not necessarily have the same pathophysiology

How can we address this?
With P4 medicine or precision medicine

Precision Medicine

"Precision medicine is like teenage sex: everyone talks about it, nobody really knows how to do it, everyone thinks everyone else is doing it, so everyone claims they are doing it"

Paraphrased from Dan Ariely, Duke University (via Dan Rader)

Basis of Uniqueness

Genetics

Microbiome

Epigenetics

Environment

Unique patient

Personalized Phenotypes

CLINICAL CHARACTERISTICS

- ± Sleepiness
- ± Co-morbidities
- Other symptoms

MOLECULAR PROFILES

- Proteomics
- Metabolomics
- Transcriptome

IN-DEPTH PHENOTYPING MEASURES

- Physiologic measures
- Imaging

Fundamental concept

- All patients with apparently the same disorder are not identical
- Use multiple approach to evaluate those differences
  - Physiological differences
  - Cliical differences
  - OMIC differences
  - Genetic and epigenetic differences
- Use unbiased, discovery approaches (clustering /machine / enhanced learning techniques)
- Likely will develop new disease classifications and systems medicine

The 4 ps

- Predictive
- Preventive
- Personalise
- Participatory

Pack AI, Ann Thoracic Soc 13: 1456, 2016

Lim DC et al Respirology 22:849, 2017

The 4 P’s

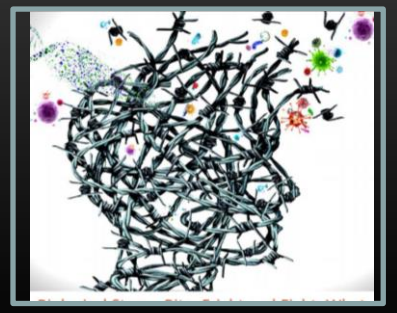
- Predictive
  - Healthy get baseline data phenotype, exercise, diet, sleep genome sequence (WGS) epigenetics all OMICs
- Preventive
  - Test improvement therapies on predictive clusters
- Personalise
  - Outcome cluster specific
- Participatory
  - use of apps, social media, new mobiles, blue tooth capabilities in intervention tools

Pack AI, Ann Thoracic Soc 13: 1456, 2016

Stratification

Stratification of orofacial pain patients?

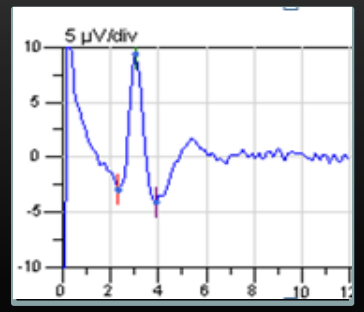
Outcomes: More accurate diagnosis, prognosis and treatment choice



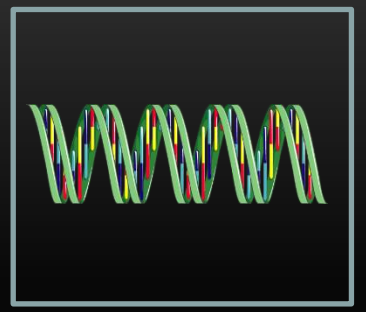
Clinical
disease or lesion, neurological deficits, family history

Psychology/ medical Co-morbidities

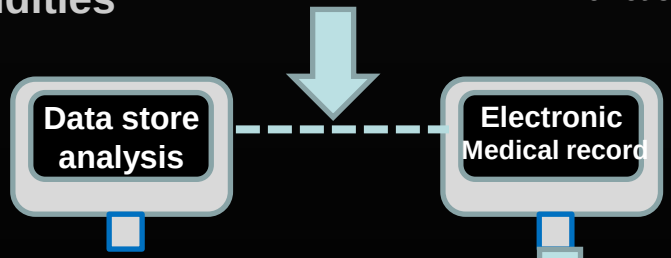
Sensory Profile
Pain quality, QST



Physiological
Electrophysiology
Functional imaging



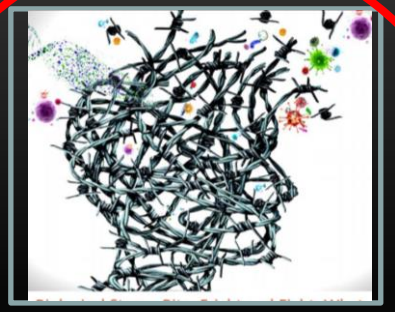
Molecular Profile OMICs
Genome, proteome, metabolome



Prof David Bennett

Stratification of orofacial pain patients?

Outcomes: More accurate diagnosis, prognosis and treatment choice



Clinical
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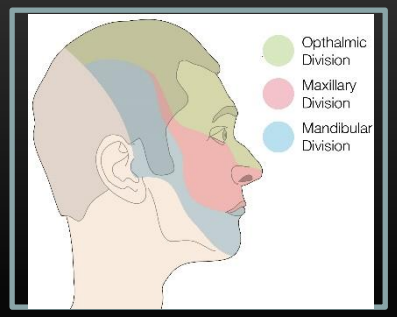
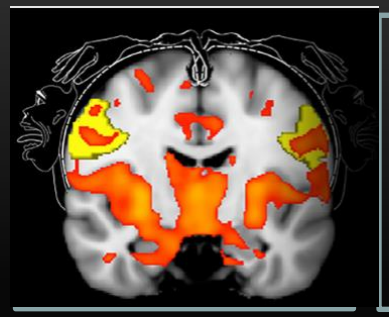


Sensory Profile
Pain quality, Qual and Quant sensory testing



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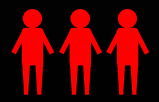
Big Data
Machine learning and Ai to improve diagnosis and clustering for treatment



Prof David Bennett

Implications of identifying pain

Comprehensive Review

August 2016 • Volume 157 • Number 8

PAIN

OPEN

Neuropathic pain: an updated grading system for research and clinical practice

Nanna B. Finnerup[a,*], Simon Haroutounian[b], Peter Kamerman[c], Ralf Baron[d], David L.H. Bennett[e], Didier Bouhassira[f,g], Giorgio Cruccu[h], Roy Freeman[i], Per Hansson[j,k], Turo Nurmikko[l], Srinivasa N. Raja[m], Andrew S.C. Rice[n,o], Jordi Serra[p], Blair H. Smith[q], Rolf-Detlef Treede[r], Troels S. Jensen[a,s]

- We can now institute screening for neuropathic pain (such as DN4 or PainDETECT).
- Better prevention measures in the field.
- Validated diagnostic tests and appropriate therapy for neuropathic pain.

Structured Pain history
SOCRATES

- Site - Where is the pain? Or the maximal site of the pain.
- **Onset –** When/ How did the pain start?
  - Was it sudden or gradual?
  - Physical or emotional?
  - Progressive or regressive?
- **C**haracter **-** What is the pain like? An ache? Stabbing? Burning? Throbbing?
- **R**adiation - Does the pain radiate anywhere? (See also Radiation.)
- **A**ssociations - Any other signs or symptoms associated with the pain?
- **T**ime course - Does the pain follow any pattern?
- **E**xacerbating/Relieving factors - Does anything change the pain?
- Severity - How bad is the pain?

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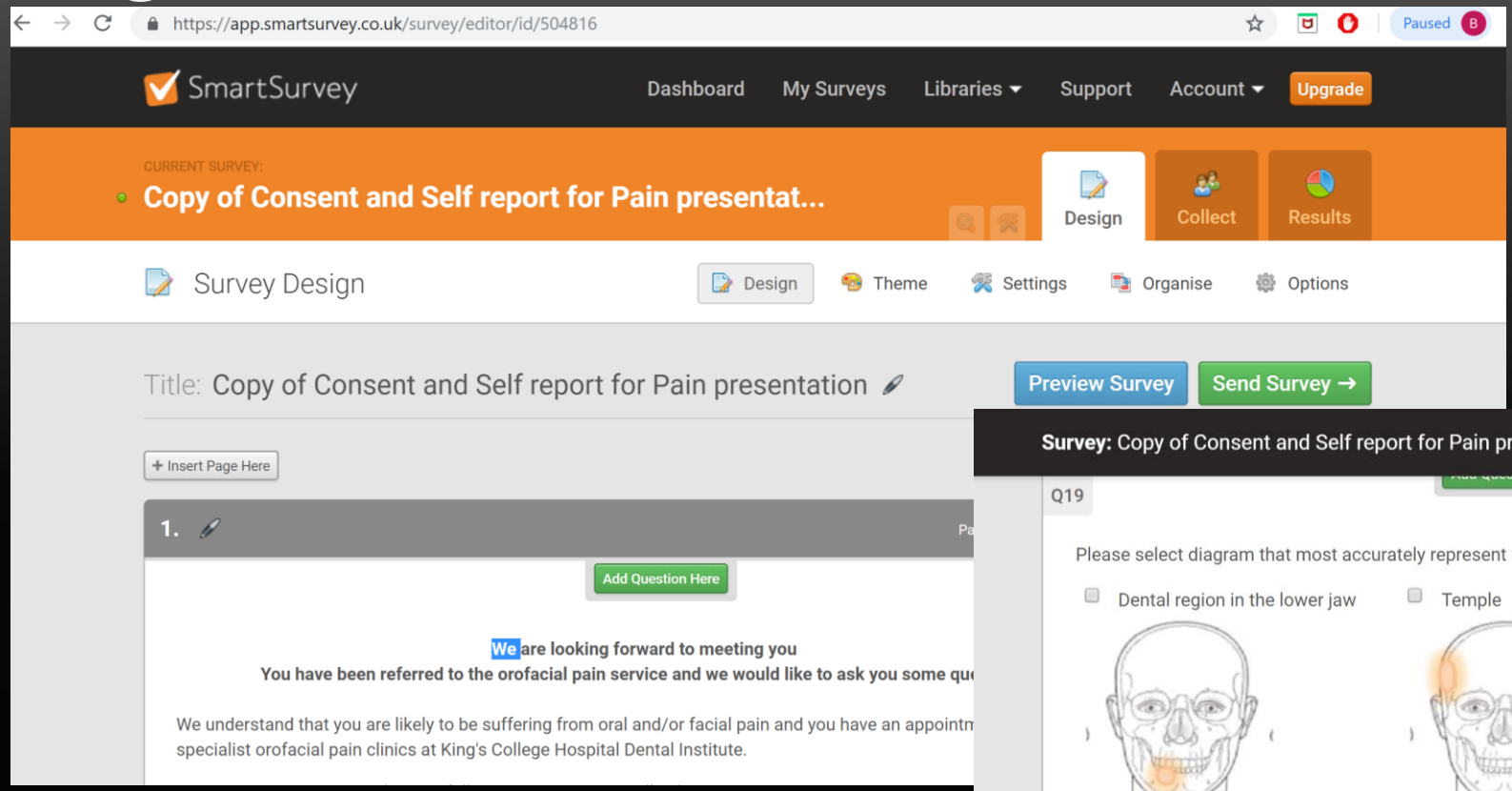
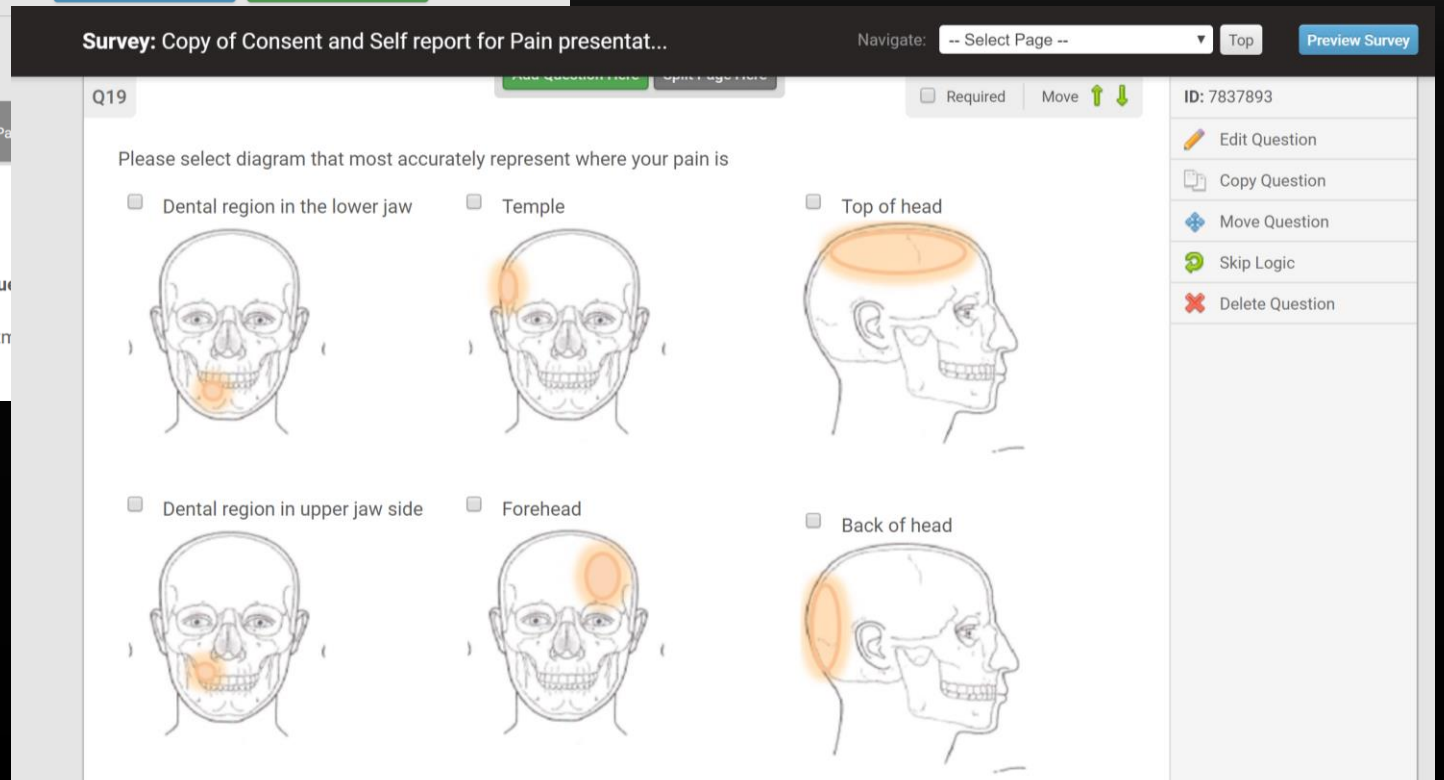
Agreed National core data set for OFP patients





Prof Justin Durham
Prof Joanna Zakrzewska

Classification OFP

International Classification of Orofacial Pain

ICOP

Version 1.0 beta

2019

Members of individual classification working groups in alphabetical order other than chair.

1. Orofacial pain associated with disorders of dentoalveolar and associated structures

Maria Pigg, Sweden (Chair); Alan Law, USA; Donald Nixdorf, USA; Tara Renton, UK; Yair Sharav, Israel

2. Orofacial pain associated with regional muscles

Peter Svensson, Denmark (Chair); Malin Ernberg, Sweden; Chris Peck, Australia

3. Orofacial pain associated with disorders of the TMJ

Per Alstergren, Sweden (Chair); Ghabi Kaspo, USA; Frank Lobbezoo, Netherlands; Ambra Michelotti, Italy

4. Orofacial pain associated with lesion/disorders of the cranial nerves and other regional nerve structures

Lene Baad-Hansen, Denmark (Chair); Eli Eliav, USA; Yoshiki Imamura, Japan

5. Orofacial pain resembling presentations of Primary Headaches

Rafael Benoliel, USA (Chair); Paulo Conti, Brazil; Arne May, Germany

6. Idiopathic orofacial pain

Thomas List, Sweden (Chair); Justin Durham, England; Jean-Paul Goulet, Canada; Satu Jääskeläinen, Finland

7. Psychosocial Assessment

Richard Ohrbach, USA

Pains of the trigeminal system

Inflammatory pain

Toothache

Abscess

TMD arthritides, Trauma, Sialadenitis, Sinusitis, mucosal disease

Nociceptive pain

Dentine sensitivity

Secondary

Neuropathic

Causes MS DM

Trigeminal neuralgia (IX,VII)

PPTTN = PDAP II)

Autonomic

Neurovascular

Primary & Secondary **Headaches**

Trigeminal Autonomic Cephalalgias (TACs)

Giant cell arteritis

Primary

Neuropathic

Neuropathic dental pain (PDAP1)

TN idiopathic

Burning Mouth

TMDs

Dysfunctional

Arthritides

Myofacial

Dysfunctional pain

Associated multiple pain conditions

LBP IBS FM

Referred pain

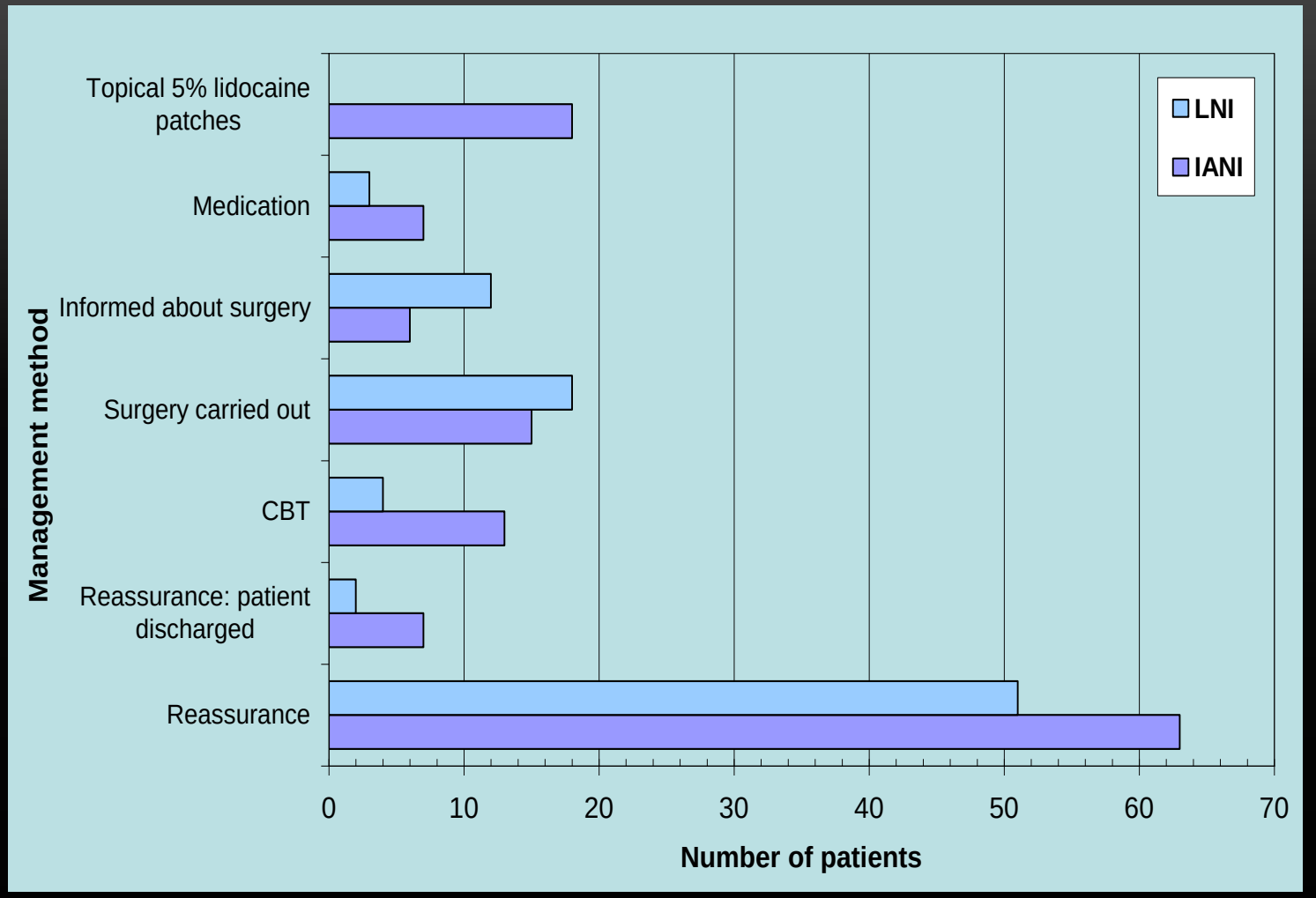
Heart

Cervical

Lung

CANCER

Response to treatment variable



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Stratification of orofacial pain patients?

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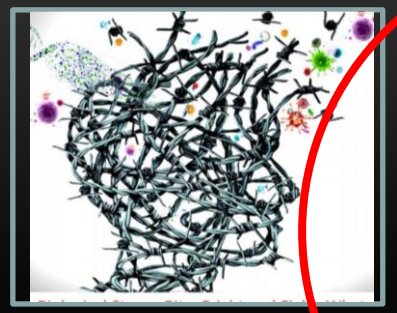

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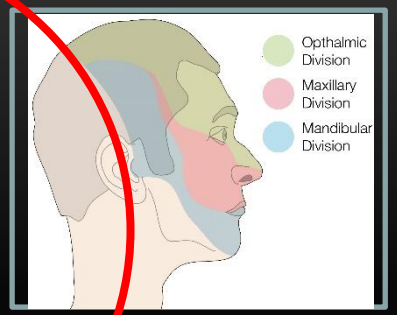

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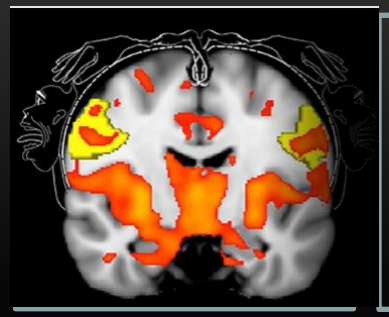

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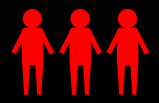
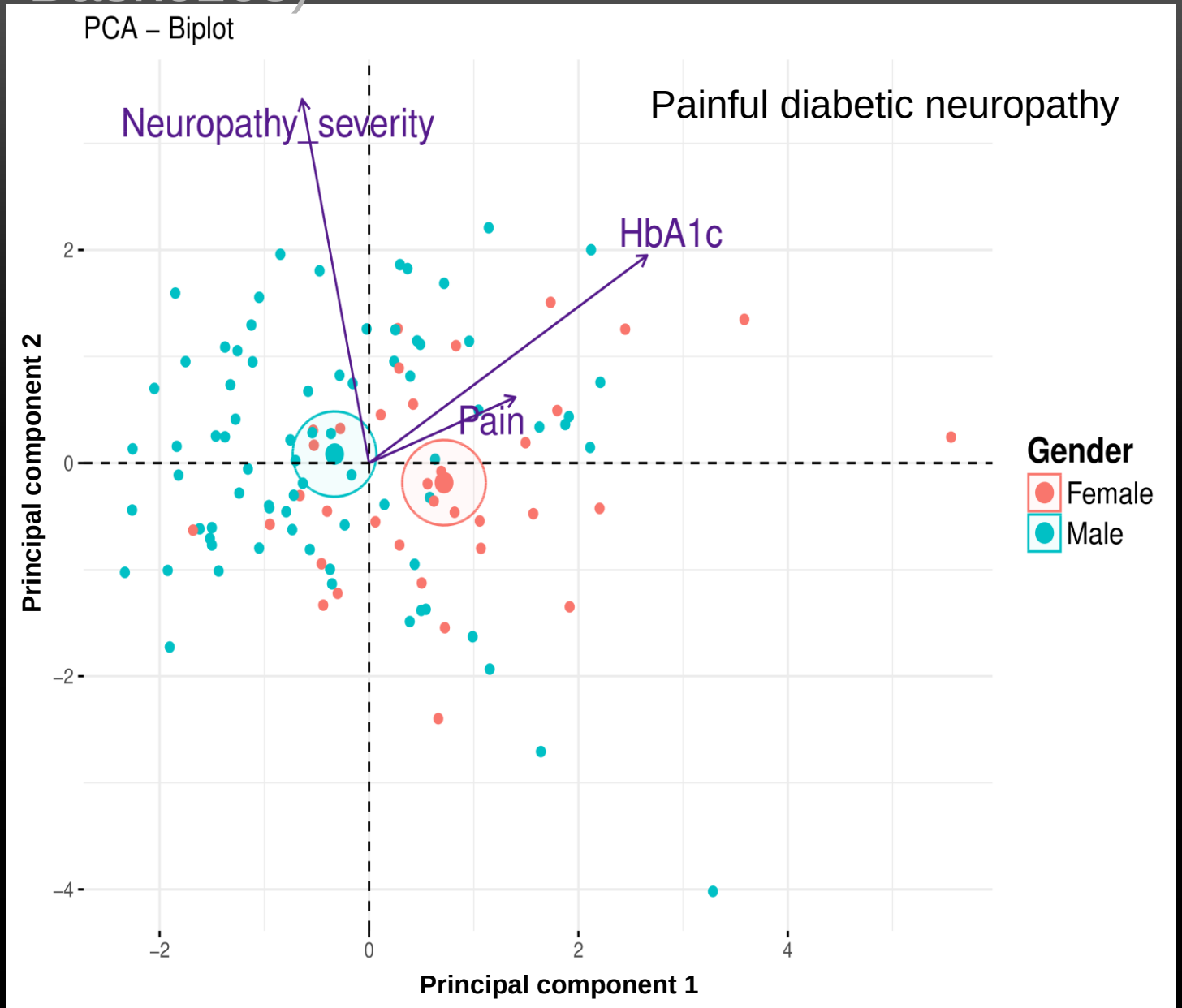


Prof David Bennett

Stratifying patients: looking at multiple factors

(D Bennett & G Baskozos)



Axis 2 and orofacial pain

Clinical Oral Investigations
October 2011, Volume 15, Issue 5, pp 749–756 | Cite as

Correlation of RDC/TMD axis I diagnoses and axis II pain-related disability. A multicenter study

Authors | Authors and affiliations

Daniele Manfredini, Jari Ahlberg, Ephraim Winocur, Luca Guarda-Nardini, Frank Lobbezoo

Original Article
First Online: 14 July 2010

Abstract

As part of an ongoing multicenter investigation involving four highly specialized tertiary clinics for temporomandibular disorders (TMD) treatment, retrospective analysis of Research Diagnostic Criteria for TMD (RDC/TMD) axis I and axis II data gathered on clinic and community cases were assessed with a twofold aim: (1) to search for a correlation between axis

ELSEVIER

The Journal of the American Dental Association
Volume 149, Issue 6, June 2018, Pages 422-431

Original Contributions
Orofacial Pain

Benefits of implementing pain-related disability and psychological assessment in dental practice for patients with temporomandibular pain and other oral health conditions

Corine M. Visscher PT, PhD, Lene Baad-Hansen DDS, PhD, Dr Odont, Justin Durham BDS, PhD, MFDS RCS Ed, FDS RCS (OS), Jean-Paul Goulet DDS, MSD, Ambra Michelotti DDS Orthod, Carolina Roldán Barraza DDS, PhD, Birgitta Häggman-Henrikson DDS, PhD, EwaCarin Ekberg DDS, Dr Odont, Karen G. Raphael PhD

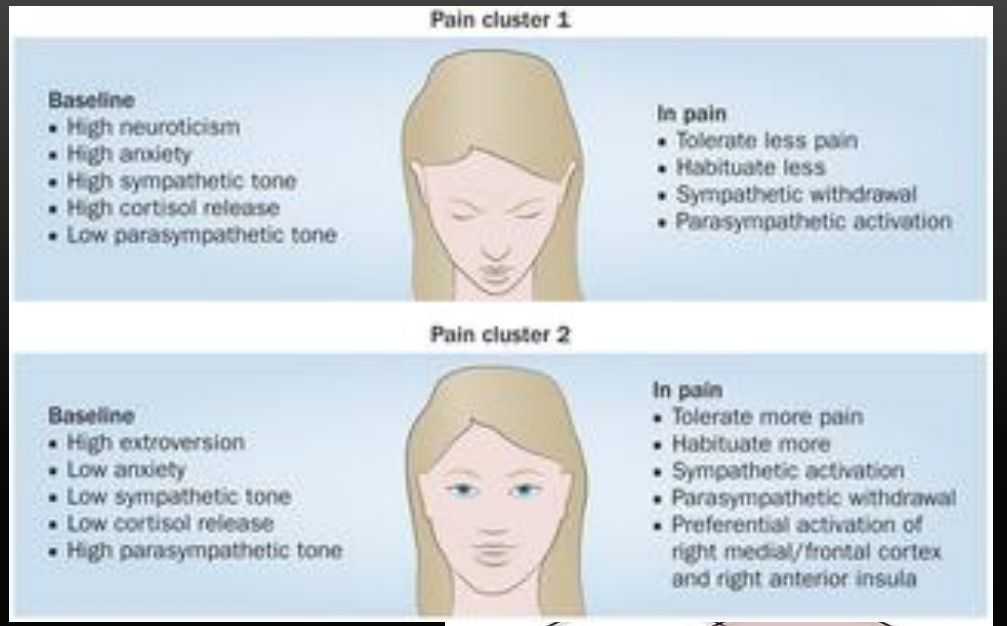
Show more

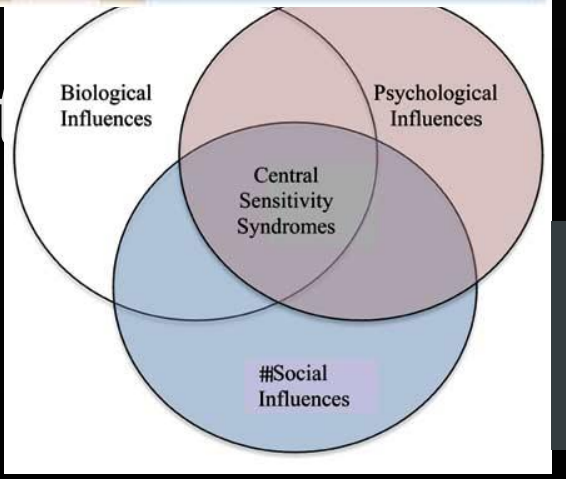
Risk factors predictive of CPSP

Psychosocial

Katz J, **Seltzer Z**. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009 May;9(5):723-44. doi: 10.1586/ern.09.20. Review.

- Cognitive
  - Fear of surgery and anxiety
  - Fear of pain
- Personality disorder
  - increased preoperative anxiety
  - Introverted personality
  - Catastrophizing
  - Poor coping skills
  - Hypervigilance state
- Psychological vulnerability – pain relat
- Social support
- Solicitous responding
  - Empathetic spouse encouraging negative behaviour
  - Munchausen





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Axis 2 Assessment of preceding and injury related psychological problems

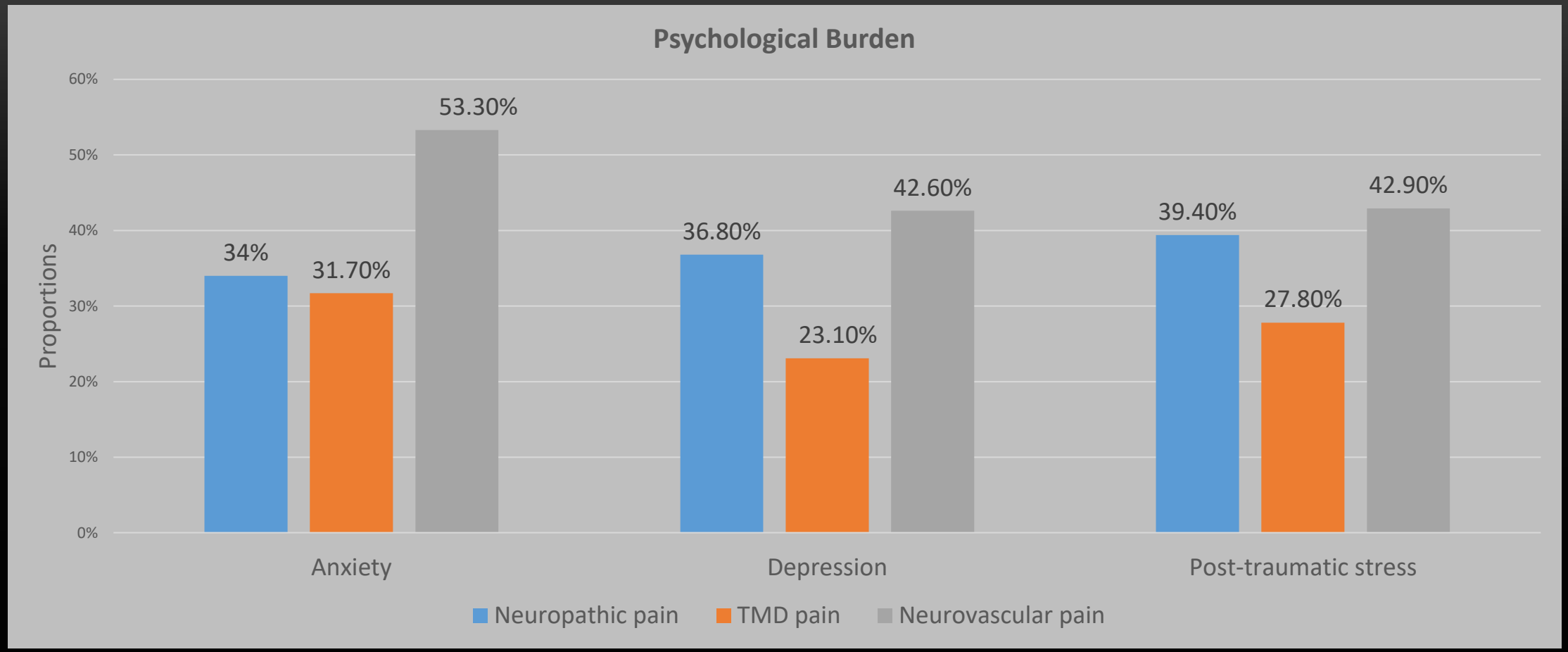
- All patients:
  - **EQ-5D**
  - **GAD7 generalised anxiety disorder**
  - **PHQ9 Patient Health Questionnaire**
  - **PHQ 15 MULTIDIMENSIONAL SCALE OF PERCEIVED SOCIAL SUPPORT**
  - **GCPS**
  - SF-MPQ-2 Short-form McGill Pain Questionnaire-2
  - PAIN DETECT PAIN QUESTIONNAIRE Ne pain
  - BPI Facial pain
  - CPSI (sleep)
  - ES-R (abuse)

- Dash board with red flags suicidal thoughts/ depression, anxiety and somatic disorders

Severe Anxiety
Probable Major depression
Somatic disorder
PTSD
Likely NP

Psychological burden of orofacial pain (n=600)

Dr Aalia Karamat PhD unpublished



2.2. Psychological impact of patients with neuropathic, musculoskeletal and neurovascular orofacial pain

Smith JG, Karamat A, Renton T
Invited paper Journal of Oral Pathology & Medicine Sept 2019

2.2.1. Abstract

Introduction: Orofacial pain (OFP) is an unpleasant sensation in the area of the face. It is commonly prevalent and produces significant level of disability and distress. Management of orofacial pain is complex and requires a multidisciplinary approach **Aims:** This study aims to evaluate the psychological impact of chronic orofacial pain (COFP) through existing standardised questionnaires and to assess the contribution of psychological function of neuropathic, musculoskeletal (TMD), neurovascular orofacial pain using standardised questionnaires incorporated in (IMPARTS) Integrating Mental and Physical healthcare: Research, Training and Services. **Methodology**: Patients between the ages of 18-80 years were recruited from the OFP clinic at Kings College Hospital London. Their demographic details were noted and psychological questionnaires were administered. According to their responses, psychological impact of OFP was assessed. **Results:** A total of 319 patients were recruited. Two hundred and thirty five (73.6%) patients were females and 84(26.3%) were males. Mean age was 48.98 years (age range from 20-80 years). Psychological questionnaires were filled by 189 (59.2%) patients. Almost 40% of individuals did not complete the questionnaires for reasons such as; questionnaires lost in the post, few individuals refuse to complete and others reported that questionnaire set was lengthy and tedious. Neuropathic pain; (Post traumatic neuropathic pain was identified in 149 (46.7%) cases, trigeminal neuralgia in 20 (6.2%), burning mouth syndrome in 6 (1.8%) cases). Temporomandibular disorders pain (TMD); were reported by 112 (35.1%) cases. Neurovascular pain; (migraine was identified in 44 (13.7%) cases, headache in 34 (10.6%) cases, trigeminal autonomic cephalalgia in 9 (2.80%) cases). Dysfunctional pain; (Persistent

Psychological·impact·of·orofacial·neuropathic·and·non-neuropathic·pain:·a·systematic·review¶

Karamat·A,·Smith·JG,·Melek·L,·Renton·T.·J·Orofacial·Pain·2019·In·Press¶

Abstract¶

Aims:·This·systematic·review·aims·to·explore·the·psychological·function·in·patients·with·neuropathic·and·non-neuropathic·orofacial·pain·conditions.·**Methods:**·A·systematic·online·search·of·Medline·(PubMed)·and·Ovid·databases·was·performed·from·2006-2016.·Observational·studies,·including·cross·sectional,·case·control·and·case·series·and·longitudinal·prospective·studies·were·included.·Search·strategy·was·restricted·to·studies·in·English·with·patients·aged·18·years·and·older.·Seventy-five·articles·were·selected.·The·standardised·PRISMA·checklist·was·used·to·report·studies·for·this·review.·Due·to·heterogeneity·across·studies,·it·was·not·possible·to·perform·meta-analyses.·**Results**·showed·that·moderate·to·severe·depression·(25.7%·-·46.7%)·and·anxiety·(51.2%·-·54.3%)·were·commonly·observed·in·patients·with·chronic·orofacial·pain·(COFP)·and·closely·linked·to·pain·severity.·Comorbid·conditions,·such·as·chronic·degenerative·disorders,·migraines·or·adverse·life·events·increased·the·likelihood·of·psychological·dysfunction·in·individuals.·Females·were·more·likely·affected·than·males.·**Conclusion:**·Assessment·of·(Axis·II)·psychological·impact·of·orofacial·pain·predominantly·focused·on·TMDs·and·rarely·on·other·conditions·including·neuropathic·or·neurovascular·pain·conditions.·More·research·is·needed·to·evaluate·the·psychological·impact·of·multiple·orofacial·pain·conditions·in·an·individual,·pre-condition·psychological·morbidity,·the·influence·of·social·factors·and·delay·in·identifying·psychological·dysfunction.¶

Key·words:·Orofacial·pain,·Neuropathic/·Non-neuropathic·pain,·TMD,·Anxiety,·Depression¶

International Journal of Oral and Maxillofacial Surgery
Volume 47, Issue 7, July 2018, Pages 869-878

Systematic Review
Oral Medicine

The psychosocial impact of orofacial pain in trigeminal neuralgia patients: a systematic review

L.N. Melek [1], M. Devine [2], T. Renton [2]

J Orofac Pain. 2013 Fall;27(4):293-303. doi: 10.11607/jop.1056.

The psychosocial and affective burden of posttraumatic neuropathy following injuries to the trigeminal nerve.

Smith JG, Elias LA, Yilmaz Z, Barker S, Shah K, Shah S, Renton T.

Abstract

AIMS: To explore the impact of trigeminal nerve injuries on quality of life, including the effect of pain on psychological and affective function.

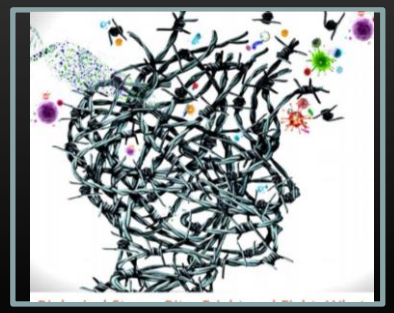
METHODS: An observational, cross-sectional survey design was employed. Fifty-six patients with inferior alveolar nerve injury (IANI) and 33 patients with lingual nerve injury (LNI) completed standardized self-report measures of pain intensity, pain catastrophizing, self-efficacy to cope with pain, and mood, in addition to generic and oral health-related quality of life (HRQoL) indicators. The impact of pain severity on these aspects of psychosocial function was examined. Summary statistics were calculated for all measures and compared with norms or values of other relevant studies, when available, using t tests. The impact of pain severity on these aspects of psychosocial function was examined using analysis of variance and hierarchical multivariate regression models.

RESULTS: The majority of patients reported pain associated with their nerve injury (86%). Nerve injury had a significant impact on all investigated domains, and this was closely linked with reported pain levels. Patients with severe pain showed particularly elevated levels of depression and pain catastrophizing, as well as substantially reduced HRQoL and coping efficacy levels. Pain intensity level was a significant predictor in all models except anxiety, uniquely contributing between 17% and 26% of variance to the prediction of pain catastrophizing, depression, coping efficacy, and generic and oral HRQoL.

CONCLUSION: Traumatic injury to the trigeminal nerve is associated with a substantial patient burden, particularly in patients who experience severe neuropathic pain as part of their condition. These findings highlight the need to identify, develop, and evaluate more effective treatments for neuropathic pain in trigeminal nerve injury that will not only provide clinically meaningful reductions in pain but also improve patients' quality of life.

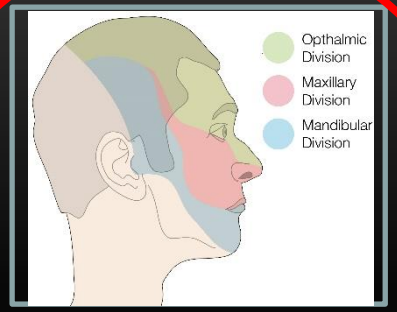
Stratification of orofacial pain patients?

Outcomes: More accurate diagnosis, prognosis and treatment choice

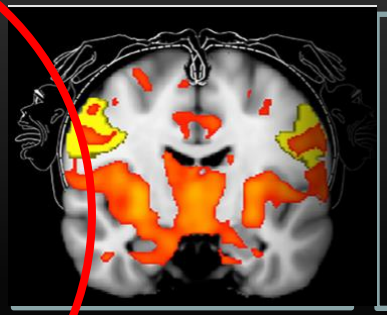


Clinical
disease or lesion, neurological deficits, family history

Psychological medical / Co-morbidities



Sensory Profile
Pain quality, Qual and Quant sensory testing



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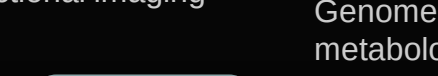
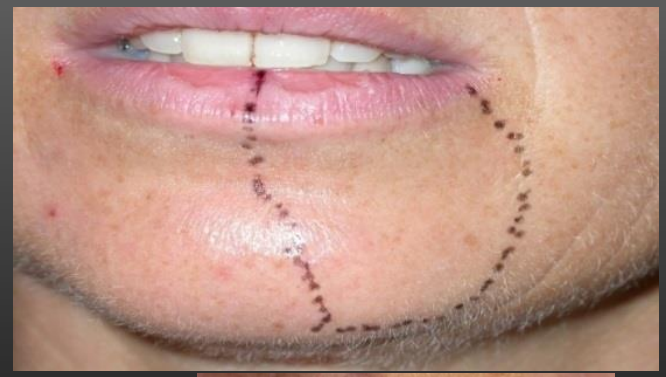
Big Data
Machine learning and Ai to improve diagnosis and clustering for treatment

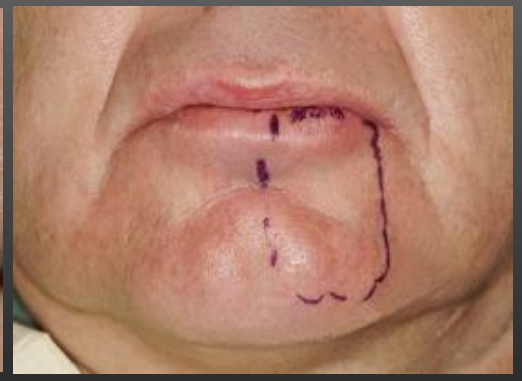


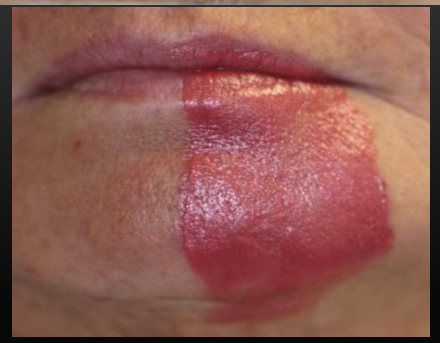
Prof David Bennett

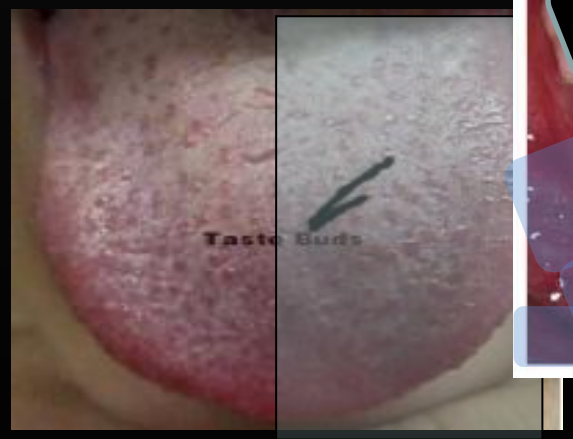
Sensory testing

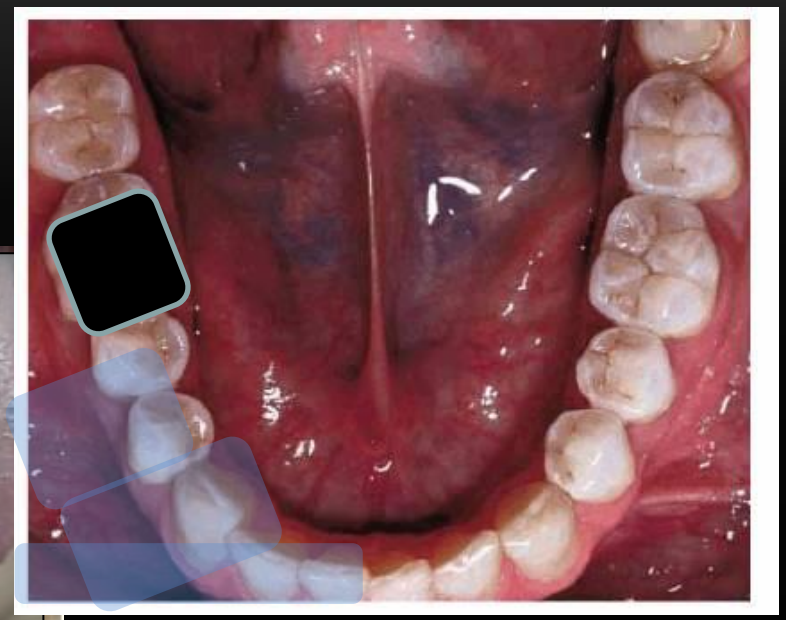
- Size neuropathic area
- Subjective function
- Thermal
- Mechanosensory LT, Sharp Blunt
    - Allodynia
    - Hyperalgesia
    - Hyperpathia
    - Spontaneous or elicited?





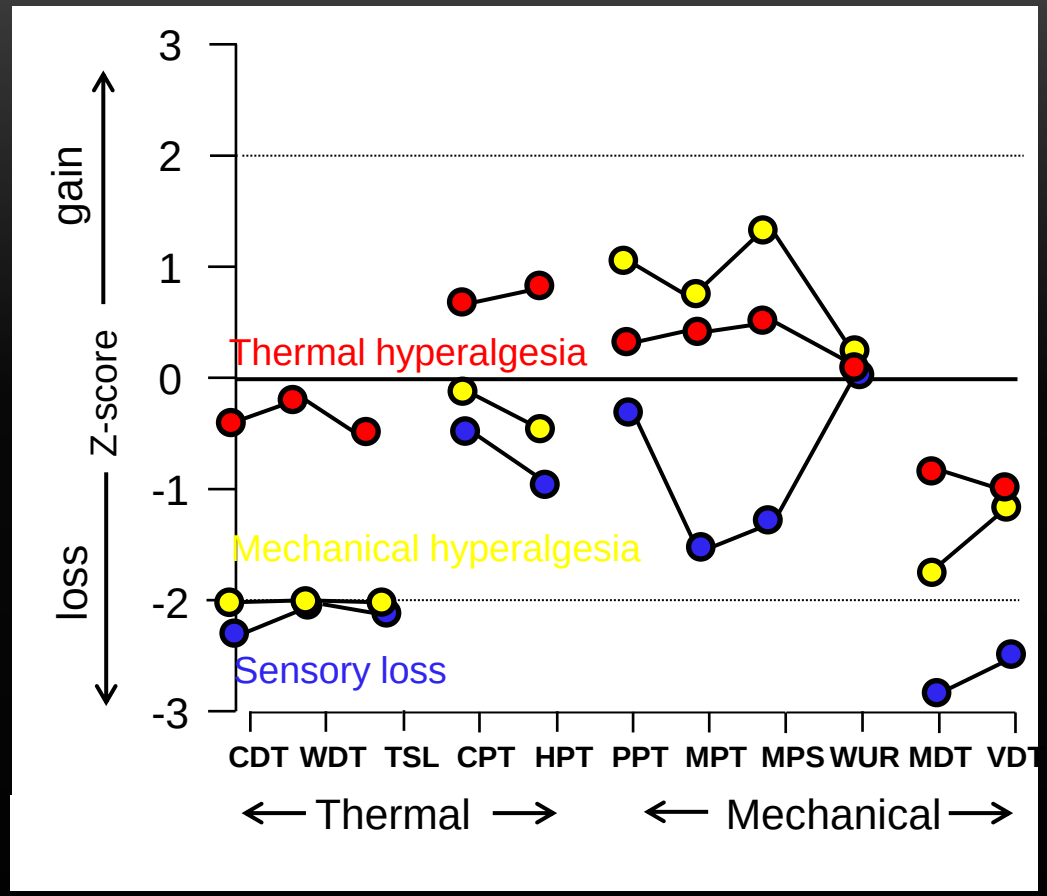


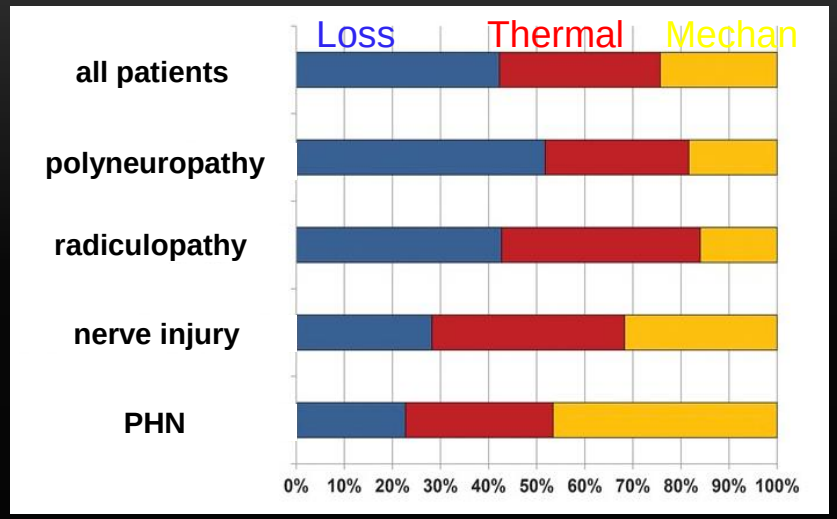




Renton T, Thexton A, SJ Crean, Hankins M. Simplifying assessment of recovery of the lingual nerve from injury. BDJ 2006 10:569-573 **Renton T**, Thexton A, Mcgurk M. New method for the objective evaluation of injury to the lingual nerve after operation on third molars.Br J Oral Maxillofac Surg. 2005 Jun;43(3):238-45. **Renton T**, Thexton A, Mcgurk M. Objective evaluation of iatrogenic lingual nerve injuries using the jaw-opening reflex. Br J Oral Maxillofac Surg. 2005 Jun;43(3):232-8

Quantitative sensory testing: Patterns of sensory dysfunction





Valet et al., Brain 2018, Baron et al., Pain 2017 and Vollert et al., Pain. 2017

J·Orofac·Pain.·2013·Spring;27(2):165-70.·doi:·10.11607/jop.1062.¶

Chairside·intraoral·qualitative·somatosensory·testing:·reliability·and·comparison·between·patients·with·atypical·odontalgia·and·healthy·controls.¶

Baad-Hansen·L[1],·Pigg·M,·Ivanovic·SE,·Faris·H,·List·T,·Drangsholt·M,·Svensson·P.¶

Abstract¶

AIMS:··To·assess·intraoral·inter-·and·intraexaminer·reliability·of·three·qualitative·measures·of·intraoral·somatosensory·function·and·to·compare·these·measures·between·patients·with·atypical·odontalgia·(AO)·and·healthy·controls.¶

METHODS:··Thirty-one·AO·patients·and·47·healthy·controls·participated.·Inter-·and·intraexaminer·reliability·was·tested·on·a·subgroup·of·46·subjects·(25·AO;·21·healthy).·Sensitivity·to·touch,·cold,·and·pinprick·stimuli·was·evaluated·on·the·painful·gingival·site·and·the·corresponding·contralateral·site·in·AO·patients,·and·bilaterally·on·the·gingiva·of·the·first·maxillary·premolars·in·controls.·Patients·were·asked·to·report·hypersensitivity,·hyposensitivity,·or·normal·sensitivity·to·stimuli·on·the·painful·site·compared·with·the·nonpainful·site.·Kappa·values·were·calculated,·and·chi-square·and·Fisher's·exact·tests·were·used·to·compare·frequencies·between·groups.¶

RESULTS:··Kappa·values·ranged·between·0.63·and·0.75.·The·frequenc·either·modality·was·significantly·higher·in·patients·(29%·to·61%)·than·in·.015),·whereas·reports·of·hyposensitivity·were·similar·between·groups·(2·Only·3.2%·of·the·AO·patients·had·no·reports·of·abnormal·sensitivity·on·a·with·59.6%·of·the·healthy·subjects·(P·<·.001).¶

CONCLUSION:··Intraoral·qualitative·somatosensory·testing·can·detect·i·disturbances·in·AO·patients,·and·the·reliability·is·sufficient·for·initial·scre·somatosensory·function.¶

J·Orofac·Pain.·2012·Spring;26(2):105-16.¶

Conditioned·pain·modulation·evoked·by·a·mechanical·craniofacial·stimulus·is·not·influenced·by·noxious·stimulation·of·the·temporomandibular·joint.¶

Oono·Y[1],·Wang·K,·Svensson·P,·Arendt-Nielsen·L.¶

Abstract¶

AIMS:··To·investigate·the·influence·of·noxious·stimulation·of·the·temporomandibular·joint·(TMJ)·on·conditioned·pain·modulation·(CPM)·and·the·possible·influence·of·gender·on·such·CPM·effects·in·the·craniofacial·region·of·humans.¶

METHODS:··Twenty·healthy·men·and·20·healthy·women·participated·in·two·sessions.·Conditioning·stimulation·(CS)·was·standardized·mechanical·stimulation·of·pericranial·muscles·at·a·pain·level·of·5·on·a·0·to·10·visual·analog·scale·(VAS).·Intra-articular·electrical·stimuli·were·applied·to·the·left·TMJ·with·an·intensity·around·VAS·=·5·(painful·session).·No·electrical·stimulation·was·applied·in·the·control·session.·Pressure·pain·threshold·(PPT)·and·pressure·pain·tolerance·threshold·(PPTol)·were·used·as·responses·to·pressure·(test)·stimuli·and·were·assessed·in·the·right·masseter·muscle·and·left·forearm·before·and·during·TMJ·stimulation·in·addition·to·the·CS·(during,·immediately·after,·and·10·minutes·after·CS).·PPT·and·PPTol·were·analyzed·by·multilevel·analysis·of·variance.¶

RESULTS:··The·parameters·were·not·dependent·on·gender,·assessment·site,·or·session,·but·were·dependent·on·time·(PPT:·PPTol;·P·<·.001)·with·session-time·interactions·(PPT:·P·<·.001,·PPTol;·P··eases·in·PPT·and·PPTol·(hypoalgesia)·in·both·sessions·and·without··tween·sessions·or·assessment·sites·during·CS·(painful·session:·49.2·±··.0·±·3.4%·for·PPT·and·painful·session:·17.7·±·3.2%,·control·session:·21.4·

oxious·stimulation·of·the·TMJ·does·not·alter·the·magnitude·of·CPM·effects··in·either·gender.·It·is·suggested·that·deficiencies·in·CPM·in·persistent··likely·more·related·to·the·duration·of·clinical·pain·than·the·pain·per·se.¶

J·Orofac·Pain.·2010·Summer;24(3):255-61.¶

Painful·conditioning·stimuli·of·the·craniofacial·region·evokes·diffuse·noxious·inhibitory·controls·in·men·and·women.¶

Wang·K[1],·Svensson·P,·Sessle·BJ,·Cairns·BE,·Arendt-Nielsen·L.¶

Abstract¶

AIMS:·To·compare·the·modulatory·effects·of·tonic·mechanical·or·thermal·craniofacial·painful·conditioning·stimuli·on·pain·sensitivity·in·craniofacial·and·spinal·test·sites·in·healthy·men·and·women.¶

METHODS:··Mechanical·and·cold·headbands·were·developed·and·tested·on·12·healthy·men·and·12·age-matched·women·(mean·+/-·SEM:·27·+/-·1.5·years).·The·pressure·applied·by·the·mechanical·headband·around·the·skull·above·the·eyebrows·could·be·adjusted·over·time·via·feedback·from·a·0·to·10·electronic·visual·analog·scale·(VAS)·to·maintain·the·pain·intensity·at·a·given·level·for·10·minutes·(3·to·7·on·VAS).·The·cold·headband·consisted·of·a·series·of·plastic·bags·filled·with·antifreeze·water·having·a·temperature·of·approx·3·degrees·C.·During·the·10·minutes·of·application,·the·subjects·were·asked·to·rate·the·pain·intensity·on·a·10-cm·VAS.·Pressure·pain·thresholds·(PPT)·were·recorded·over·the·right·and·left·masseter·muscles·(MAR,·MAL),·right·splenius·muscle·(neck),·right·elbow·(elbow),·and·right·middle·finger·(finger)·by·a·pressure·algometer·(1-cm2·area·probe).·The·PPTs·at·each·of·the·five·sites·were·determined·at·baseline·and·during·the·mechanical·or·cold-induced·pain.·The·two·sessions·with·mechanical·or·cold·headbands·were·performed·at·an·interval·of·30·minutes.¶

RESULTS:·Women·had·significantly·lower·absolute·PPT·values·than·men·at·most·test·sites·(Unpaired·t-test:·P·<·.027).·The·mechanical·headband·caused·pain·in·both·men·(peak·pain·mean·+/-·SEM:·4.7·+/-·0.4·cm)·and·women·(4.9·+/-·0.4·cm)·(P·=·.455).·A·significant·PPT·elevation·was·found·at·MAR,·MAL,·neck,·and·finger·in·men·(11%·to·17%;·P·<·.031)·and·at·MAR,·MAL,·and·neck·in·women·(15%·to·22%;·P·<·.020)·during·the·mechanical-induced·pain.·The·cold·headband·caused·

Stratification of orofacial pain patients?

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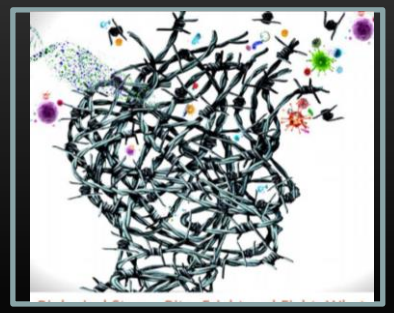

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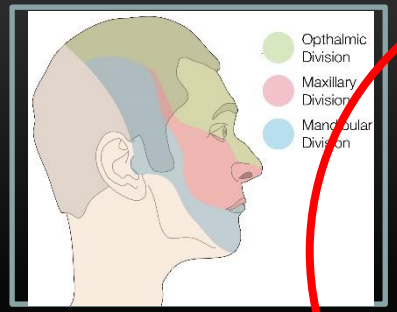

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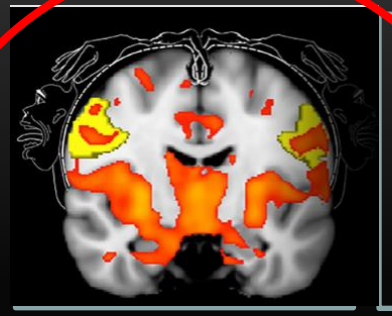

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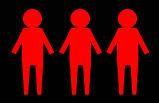

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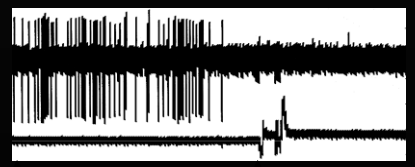
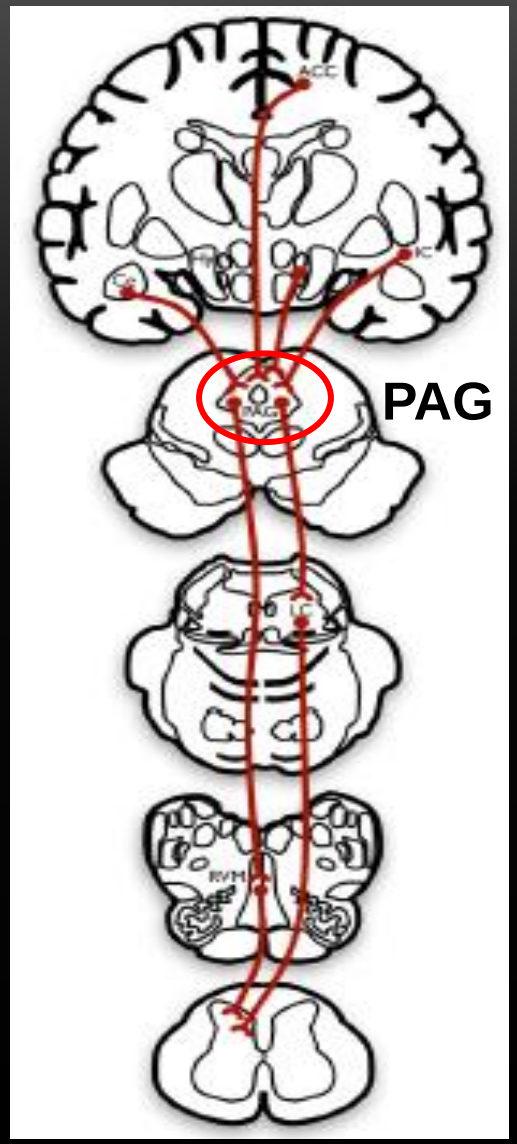
Descending pain modulation

Off-Cell



Opioids
Noradrenaline
5HTR 1/7

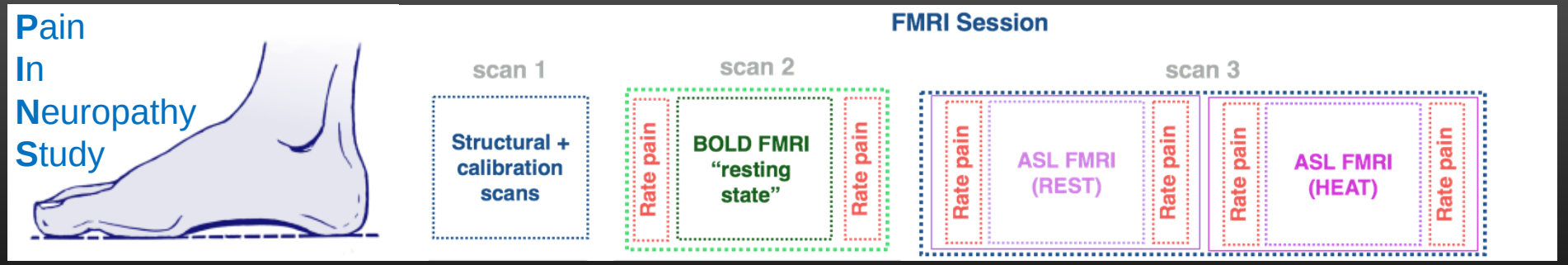


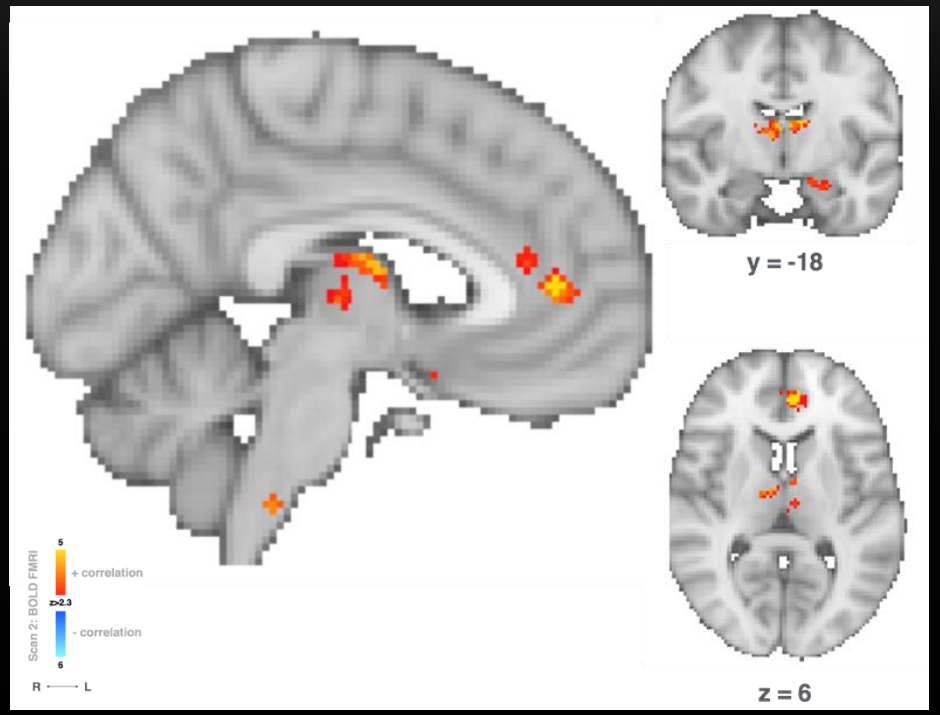
West et al., Neuroscience 2015

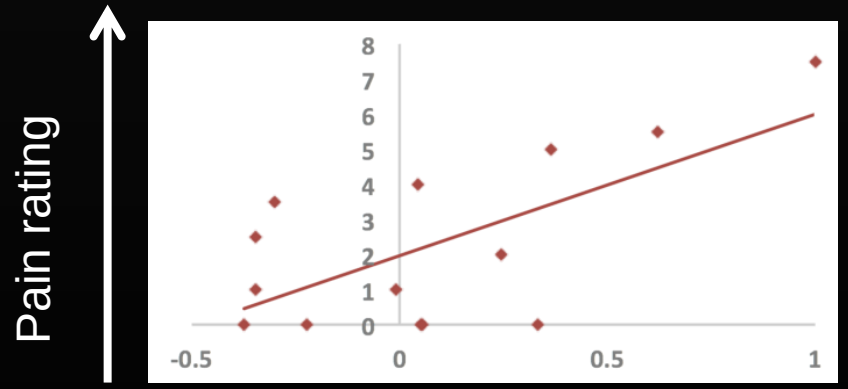
On-Cell

5HTR 2/3

fMRI provides insight to descending pain modulation in painful diabetic neuropathy (I Tracey and A Segerdahl)





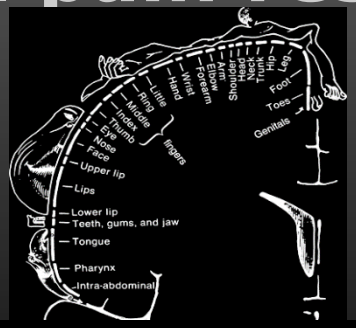


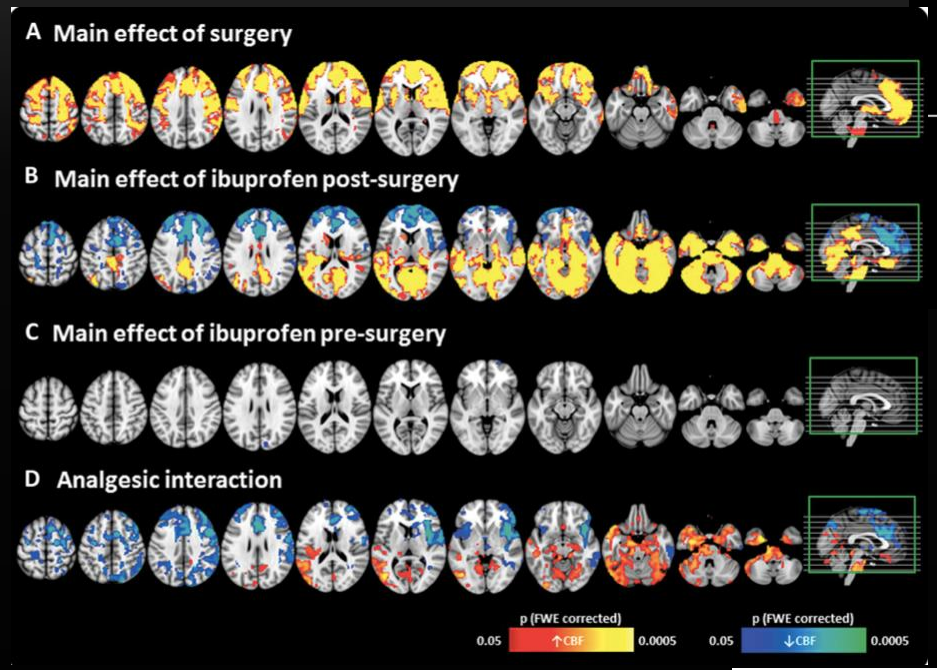
Correlation between vlPAG and regions in red

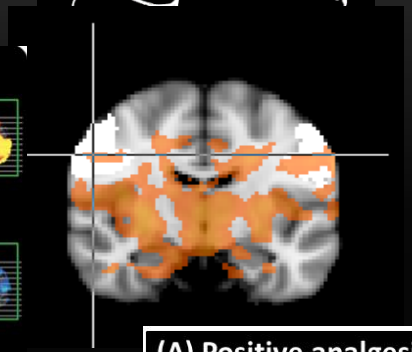
Segerdahl et al (2018) Brain

Using magnetic resonance arterial spin labelling we can evaluate central pain response in patients?

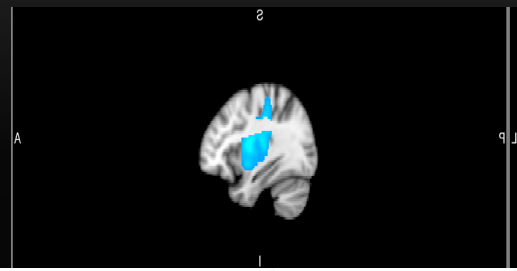
- Post wisdom teeth surgery = inflammatory pain
- Where does paracetamol and ibuprofen work centrally?

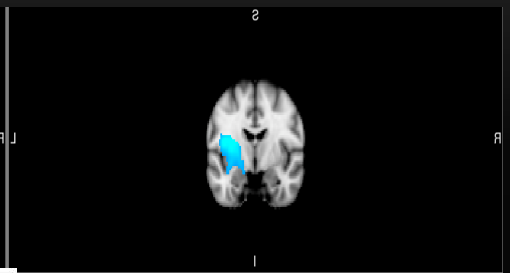


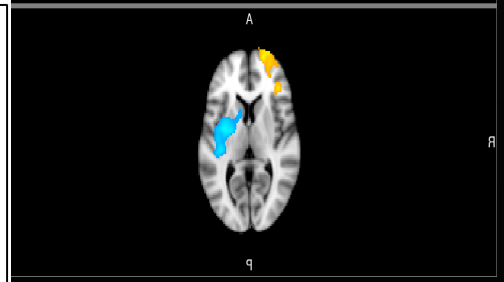


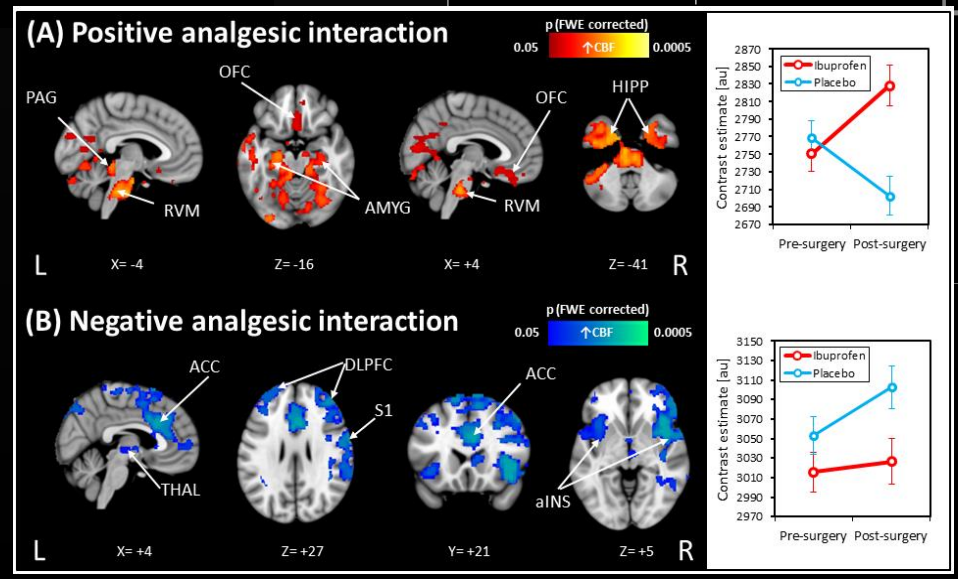


- Evaluating central modulation of pain using post wisdom teeth surgery pain and Orofacial neuropathic pain
- LA block interrupting ongoing pain
- QST assessing MA and CA







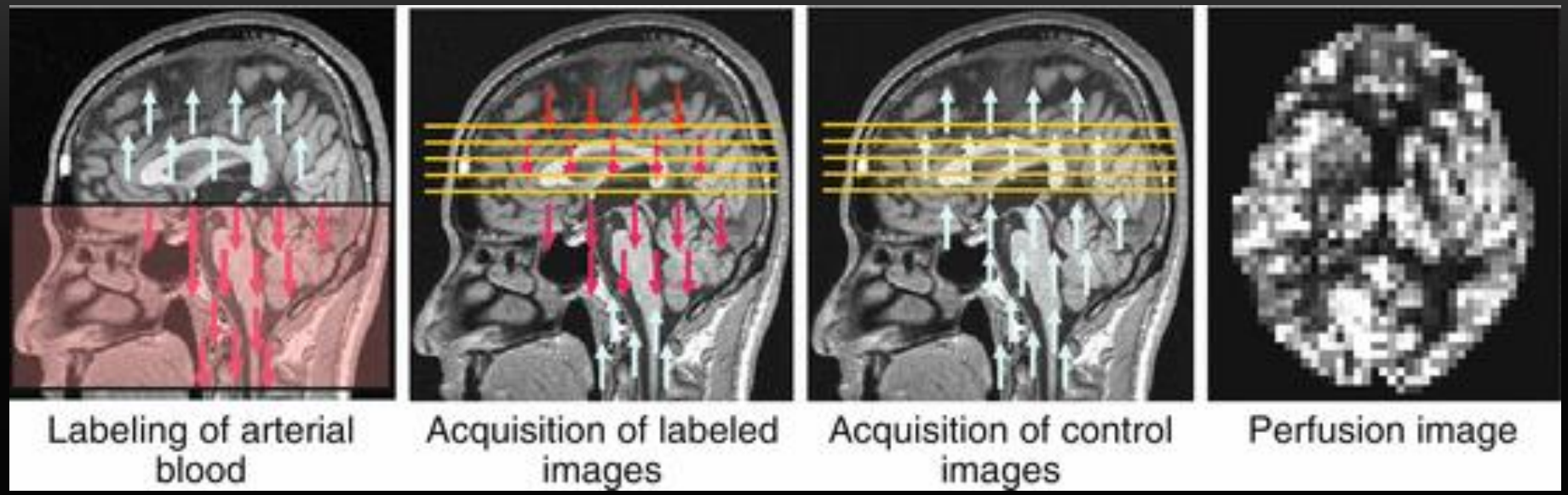


Dr Nadine Khawaja,
Dr Matt Howard IoPPN CNS

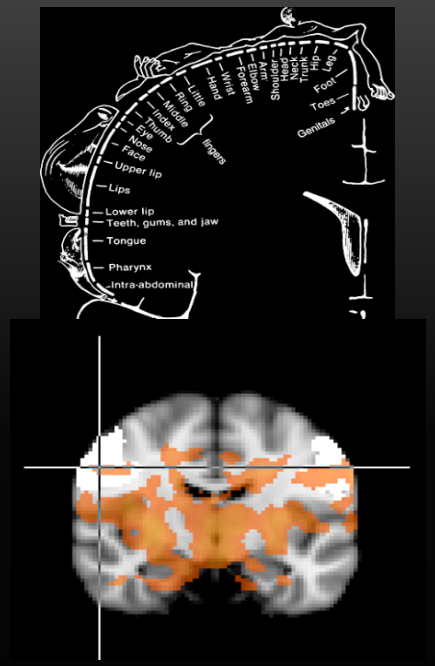
gsk

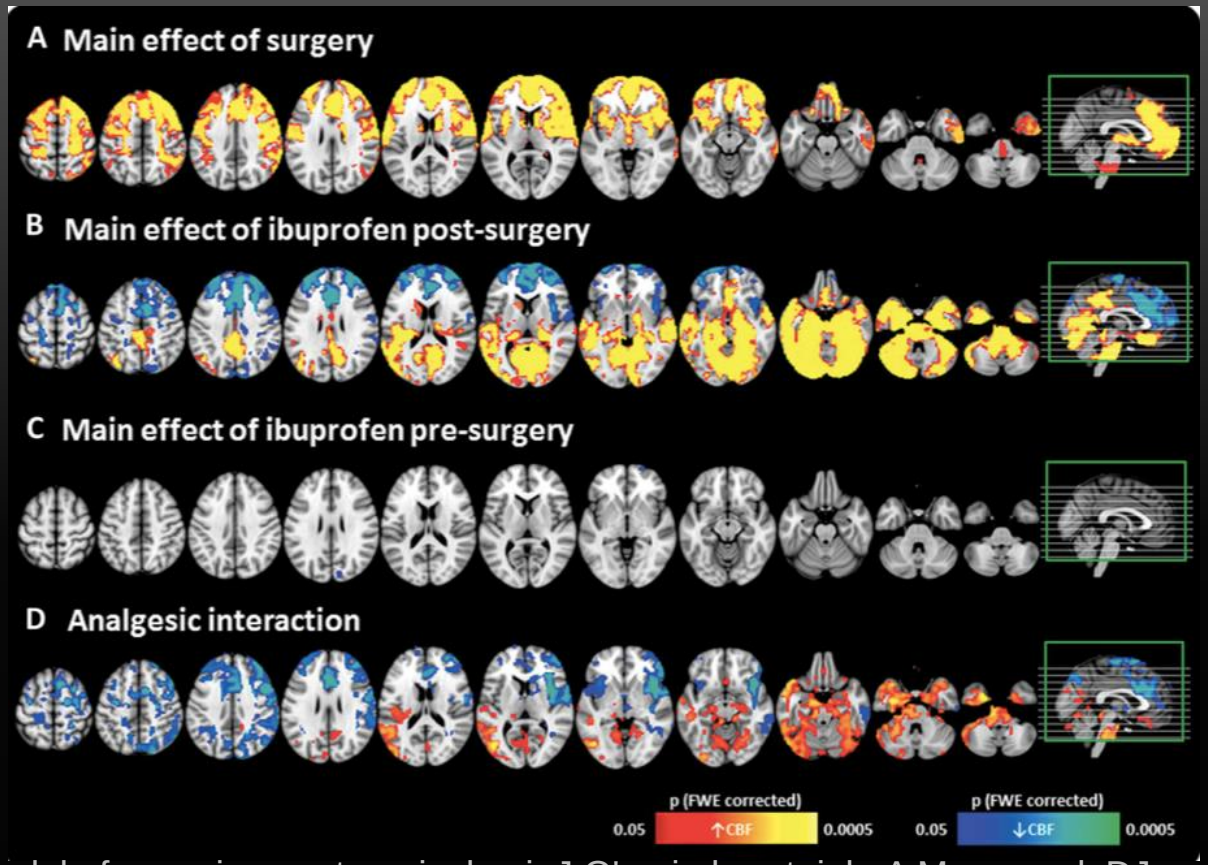
MRC Medical Research Council

Arterial spin labelling



Application of Arterial spin labelling to central post surgical trigeminal pain



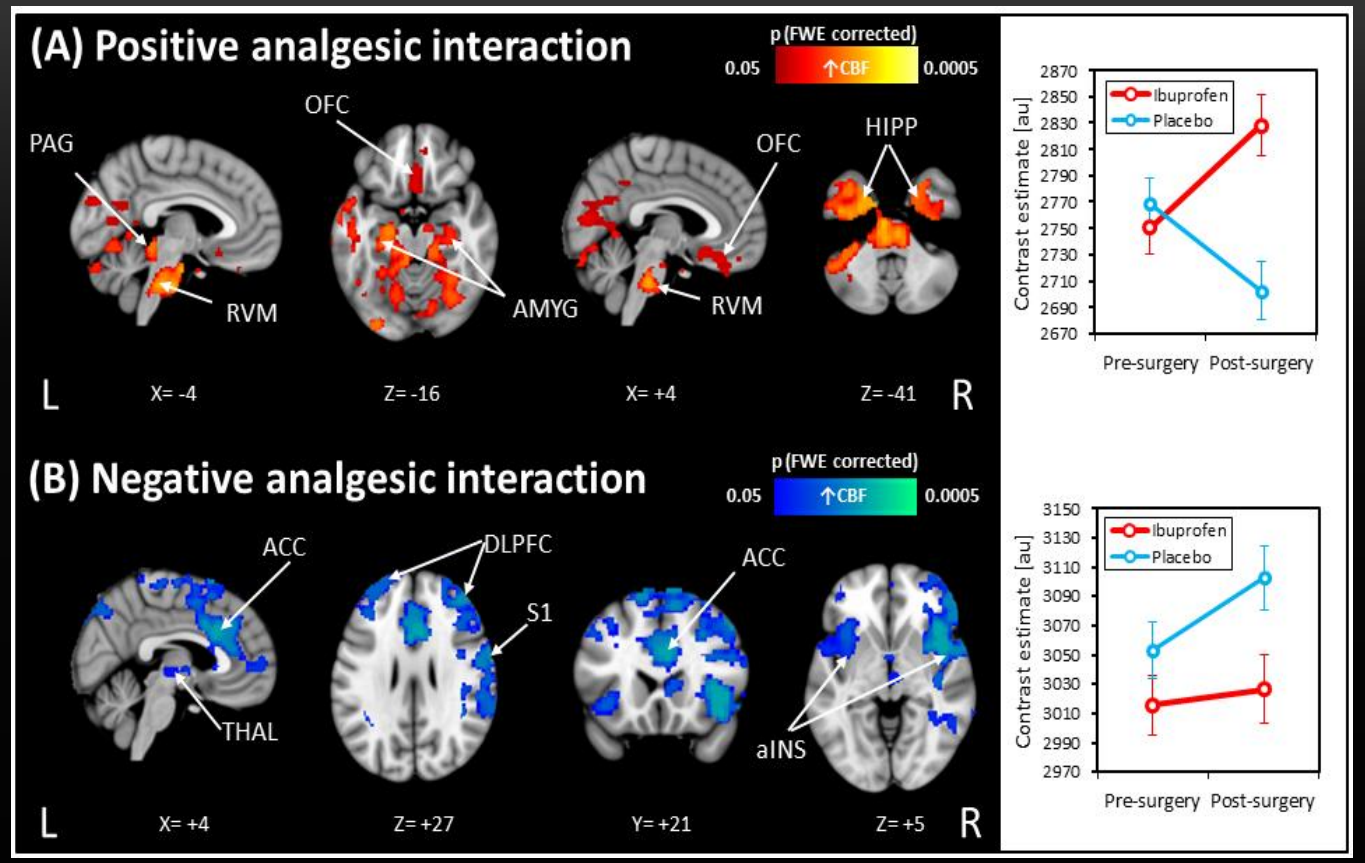


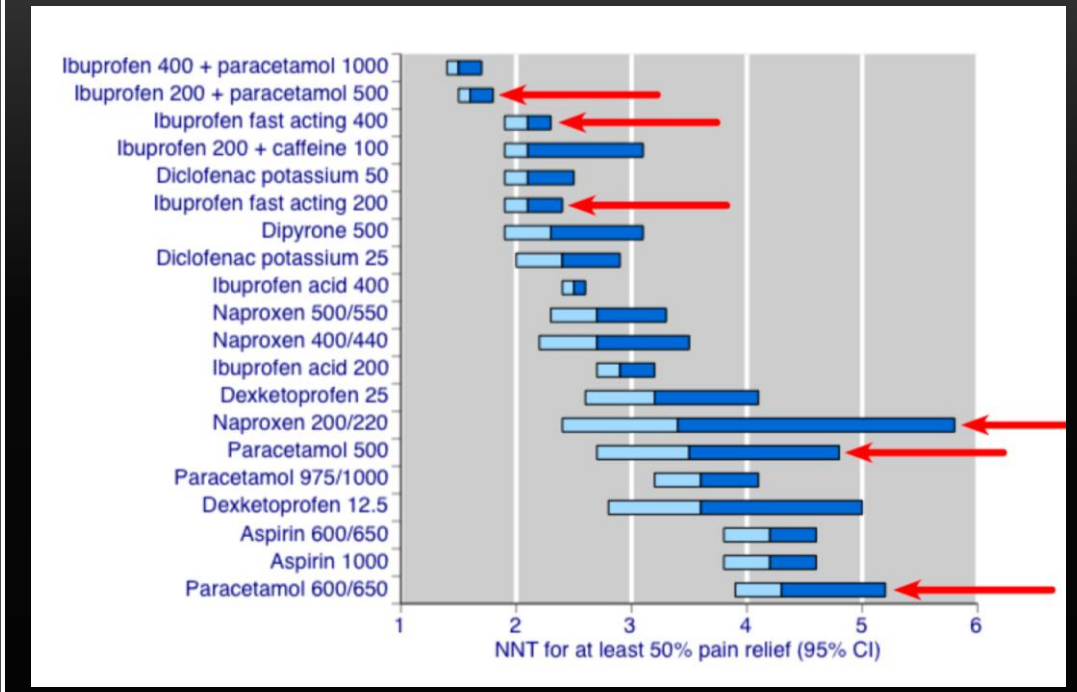
Multivariate decoding of cerebral blood flow measures in a clinical model of on-going postsurgical painJ O'muircheartaigh, A Marquand, DJ Hodkinson, K Krause, N Khawaja, ...Human brain mapping 36 (2), 633-642

Cerebral analgesic response to nonsteroidal anti-inflammatory drug ibuprofenDJ Hodkinson, N Khawaja, O O'daly, MA Thacker, FO Zelaya, ... Pain 156 (7), 1301-131. Quantifying the test–retest reliability of cerebral blood flow measurements in a clinical model of on-going post-surgical pain: A study using pseudo-continuous arterial spin …DJ Hodkinson, K Krause, N Khawaja, TF Renton, JP Huggins, W Vennart, ... NeuroImage: Clinical 3, 301-310. Beyond patient reported pain: perfusion magnetic resonance imaging demonstrates reproducible cerebral representation of ongoing post-surgical painMA Howard, K Krause, N Khawaja, N Massat, F Zelaya, G Schumann, ... PloS one 6 (2), e17096

Application of Arterial spin labelling to central post surgical trigeminal pain

Synergism of paracetamol and Ibuprofen



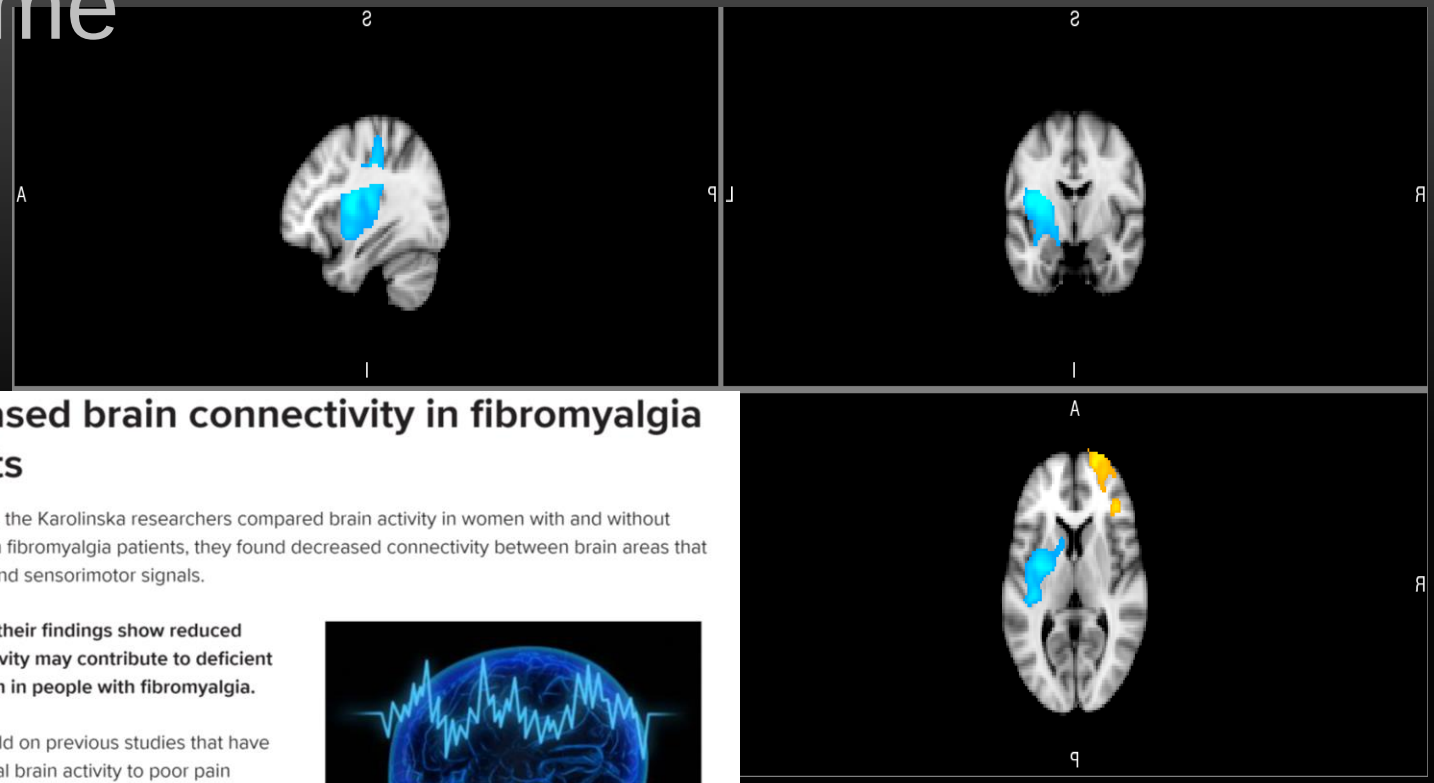


MRC Medical Research Council

Application of Arterial spin labelling to central post surgical trigeminal pain Burning mouth syndrome

Loss of brain connectivity in patients with burning mouth syndrome

Dr Kiran Beneng, Dr Matt Howard
IoPPN CNS



Decreased brain connectivity in fibromyalgia patients

For their study, the Karolinska researchers compared brain activity in women with and without fibromyalgia. In fibromyalgia patients, they found decreased connectivity between brain areas that process pain and sensorimotor signals.

They suggest their findings show reduced brain connectivity may contribute to deficient lation in people with fibromyalgia.

s build on previous studies that have ormal brain activity to poor pain

udy, 22 healthy women and 16 with gia underwent functional magnetic e imaging (fMRI) brain scans while ing different levels of pain by having

MENU

nature neuroscience

Brief Communication | Published: 01 July 2012

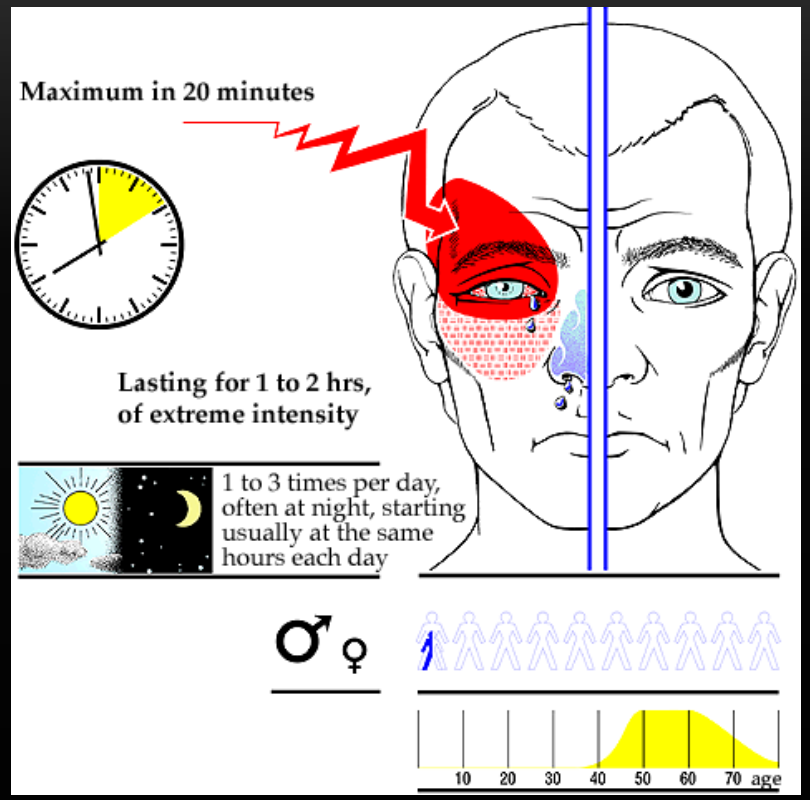
Corticostriatal functional connectivity predicts transition to chronic back pain

Marwan N Baliki, Bogdan Petre, Souraya Torbey, Kristina M Herrmann, Lejian Huang, Thomas J Schnitzer, Howard L Fields & A Vania Apkarian

Nature Neuroscience **15**, 1117–1119 (2012) | Download Citation

MRC Medical Research Council

Application of Arterial spin labelling to trigeminal pain Cluster headache



Title

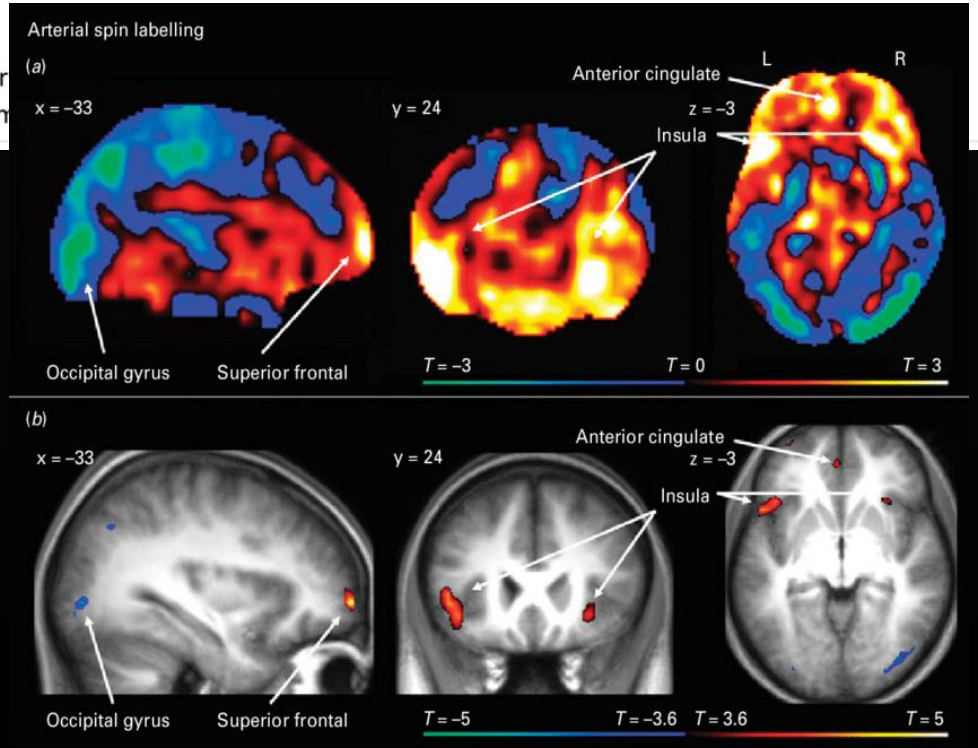
Changes in Brain Structure and Function in Cluster Headache and Predictors for Treatment Response

Sonia Medina[1,2], Owen O'Daly[1], Elena Makovac[1,2], Norazah A Bakar[3], Sarah Miller[4], Tara Renton[3], Steve CR Williams[1], Manjit Matharu[4], Matthew A Howard[1]

[1] Department of Neuroimaging, King's College London
[2] Wolfson Centre for Age-Related Diseases, King's College London
[3] Department of Oral Surgery, King's College London
[4] UCL Institute of Neurology, Queen Square, London

Introduction

Cluster headache (CH) is a pr
Despite several functional in



Application arterial spin labelling applied to assess pain modulation

CPMS Study Details Request Form

Please fully complete this form. The information requested is necessary for the Portf
record in CPMS.

IRAS ID	254806	Acronym/Short title	Descending modulation and central s

1. Provide information regarding the organisation(s) funding the study in the table belo

Funding Organisation	Medical Research Council	Grant c

Title of study: Investigating Mechanisms Of Ongoing Peripheral Drive, Central Sensitisation And Endogenous (Descending) Pain Modulation In Patients With Chronic Painful Iatrogenic Inferior Alveolar Nerve Injury.

Short Title: Descending modulation and central sensitisation in postsurgical neuropathic pain

Study Acronym: CPMNP

Therapeutic Area: Pain

Version and Date: Version 3 and 27/11/2018

IRAS ref: 254806

GIVE FEEDBACK

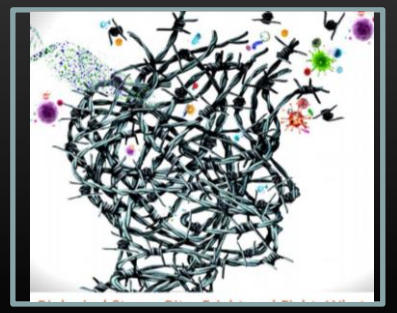
Date of completion: 21/12/2018

Study Title:	Mechanisms of ongoing peripheral drive, central sensitisation and endogenous (descending) pain modulation in a post-surgical pain model following a lower alveolar nerve injury with neuropathic pain.
Short Title/Acronym:	Descending modulation and central sensitisation in neuropathic pain
Sponsor Institution:	King's College Hospital & King's College London
Funder:	Medical Research Council (MRC) Grant ref: MR/N026969/1
IRAS number:	254806
Chief Investigator:	Prof. Tara Renton

MRC Medical Research Council

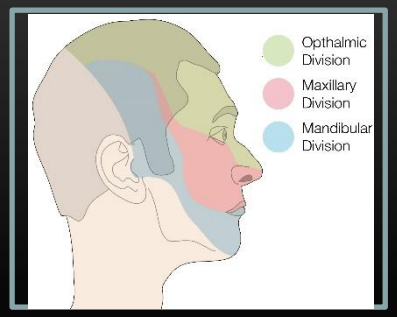
Stratification of orofacial pain patients?

Outcomes: More accurate diagnosis, prognosis and treatment choice

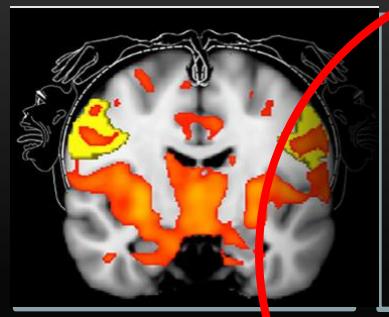


Clinical
disease or lesion, neurological deficits, family history

Psychological medical / Co-morbidities



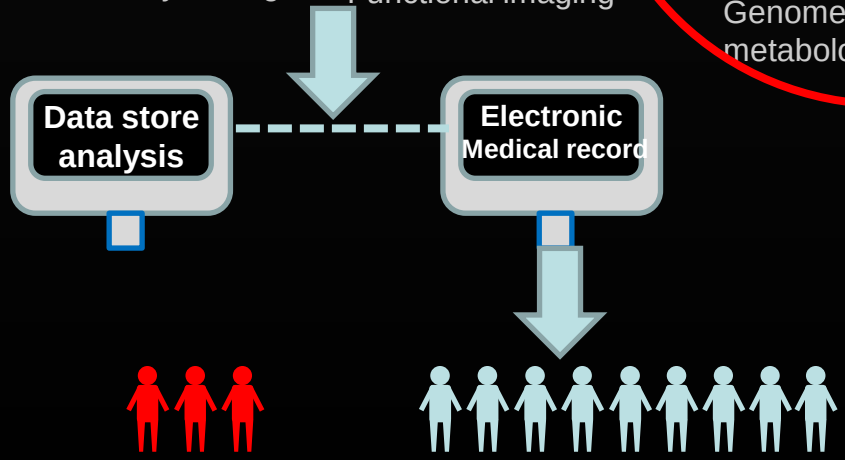
Sensory Profile
Pain quality, Qual and Quant sensory testing



Physiological
Electrophysiology
Functional imaging

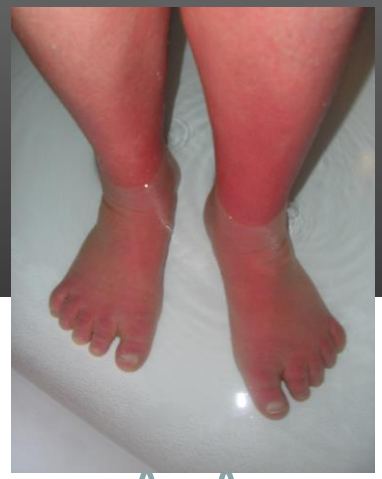
Molecular Profile OMICs
Genome, proteome, metabolome

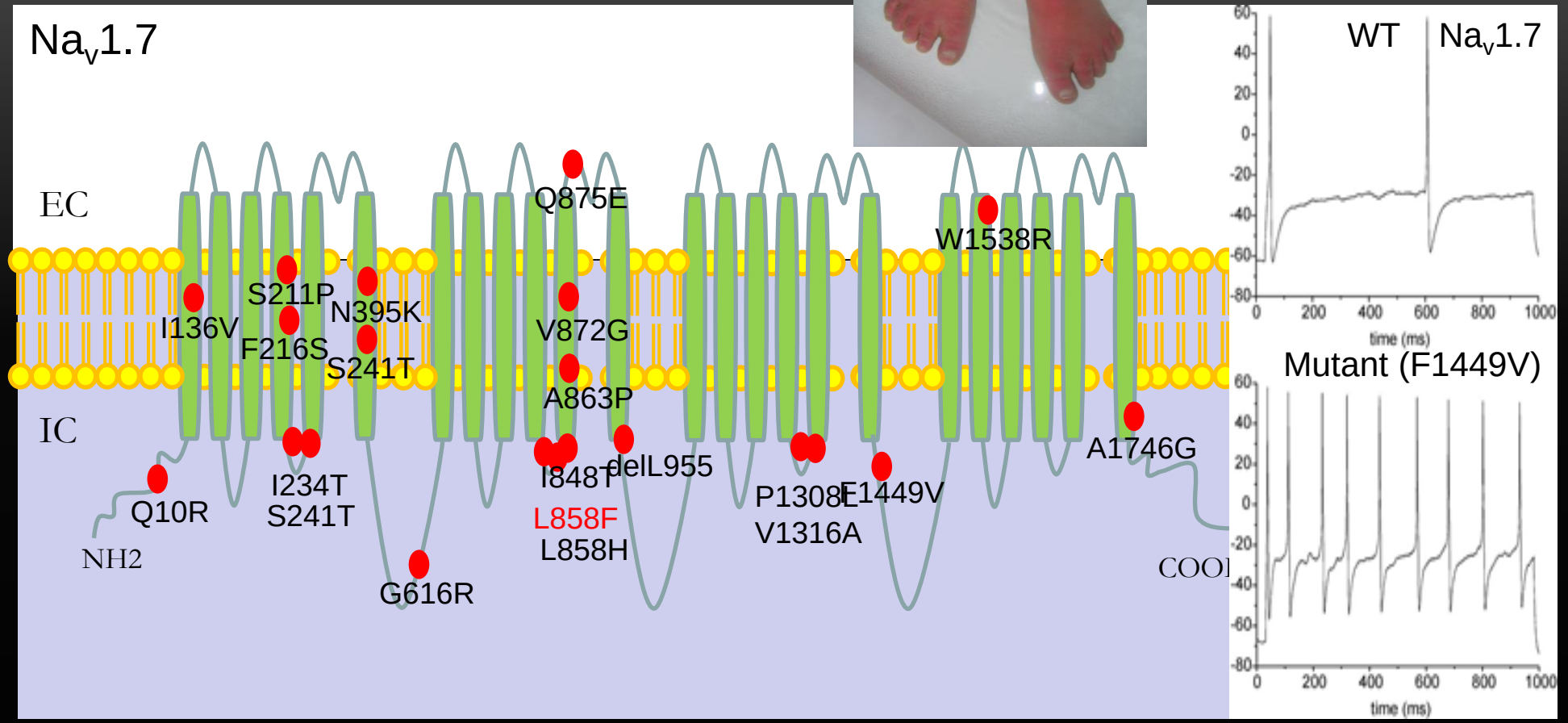
Big Data
Machine learning and Ai to improve diagnosis and clustering for treatment



Prof David Bennett

Mendelian pain disorders: Inherited erythromelalgia



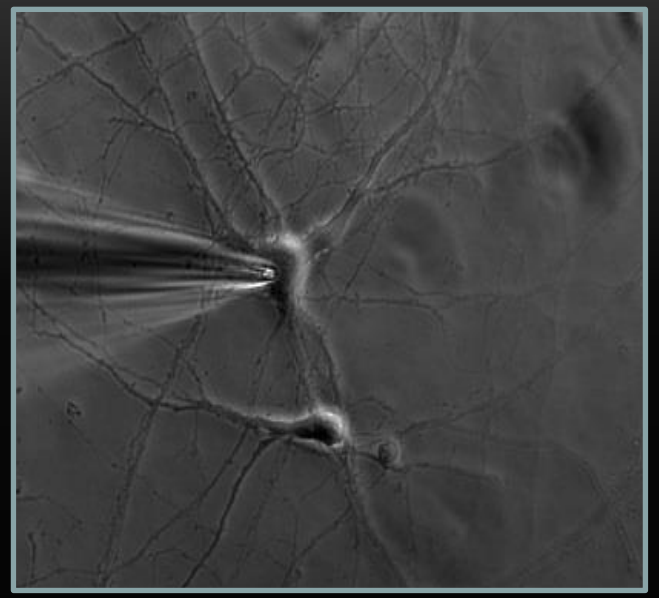


Dib-Hajj et al., Brain 2005

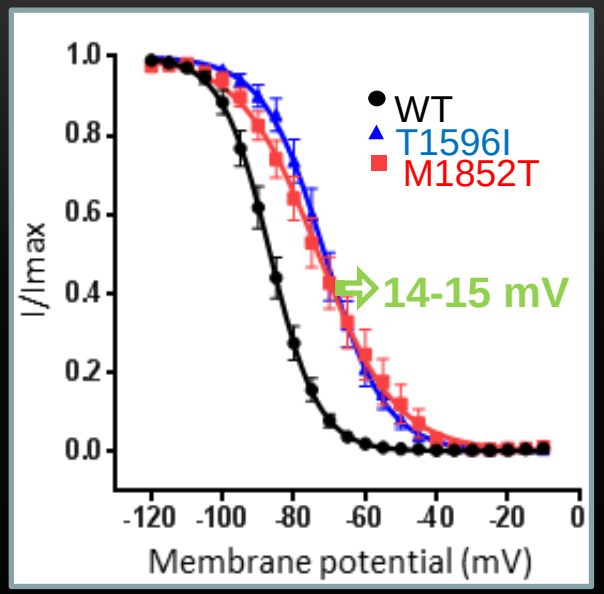
Na 1.7 rare variants enhance excitability

Blesneac et al., Pain 2018

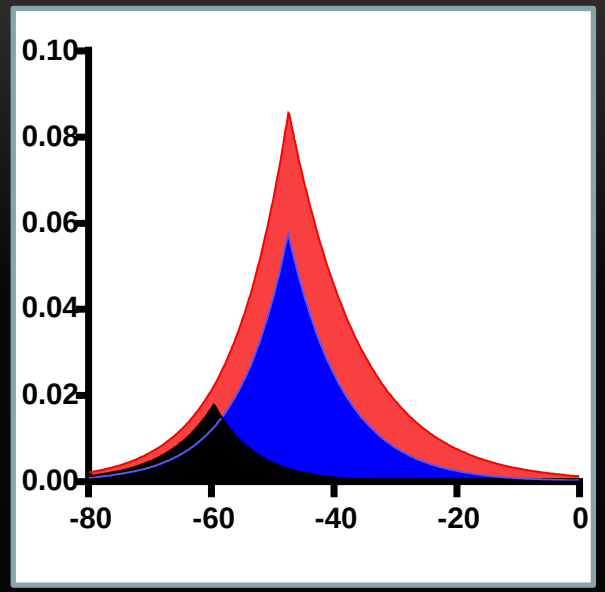
Patch clamp analysis



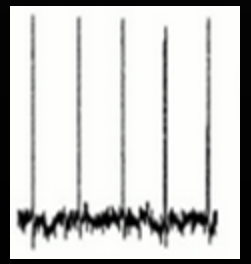
Altered fast inactivation



Window current

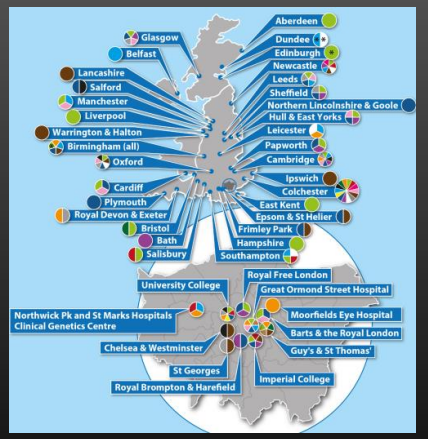


Gain of function

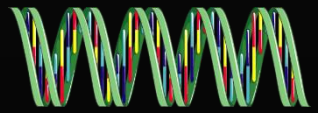


Whole genome sequencing in clinical practice

BRIDGE



193 participants recruited
(confirmed neuropathic pain)



Whole genome sequencing

143 rare variants identified in NeuPain genes

26 variants of clinical significance

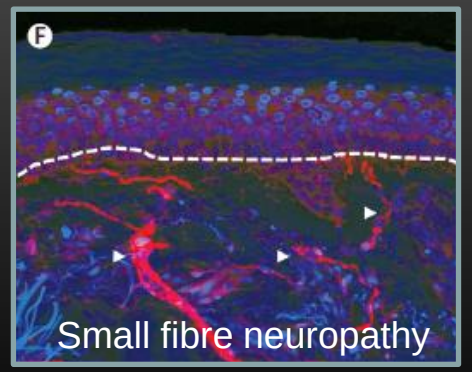
Better patient stratification to target treatment

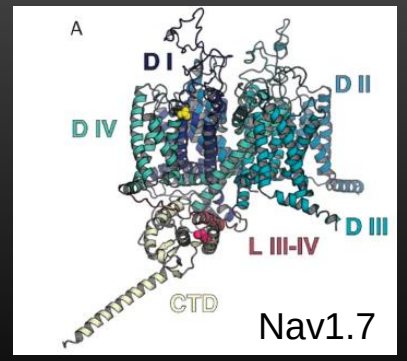
Stratification based on genotype:

STUDY PROTOCOL Open Access

Efficacy, safety, and tolerability of lacosamide in patients with gain-of-function $Na_v1.7$ mutation-related small fiber neuropathy: study protocol of a randomized controlled trial–the LENSS study

Bianca T. A. de Greef[1*], Ingemar S. J. Merkies[1,2], Margot Geerts[1], Catharina G. Faber[1] and Janneke G. J. Hoeijmakers[1]





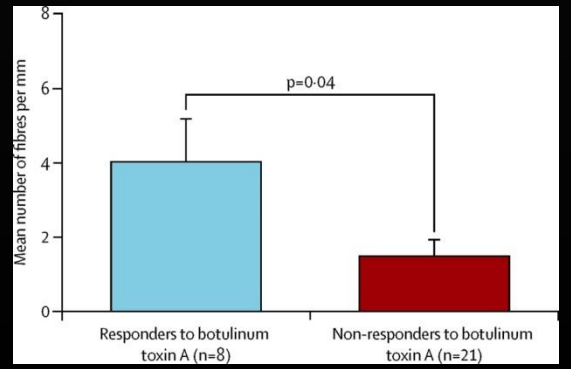
I Merkies and K Faber (presented PNS 2017)

The relationship of innervation density to treatment response:

Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial

Nadine Attal, Daniel C de Andrade, Frédéric Adam, Danièle Ranoux, Manoel J Teixeira, Ricardo Galhardoni, Irina Raicher, Nurcan Üçeyler, Claudia Sommer, Didier Bouhassira

Lancet Neurol 2016; 15: 555–65
Published Online February 29, 2016
http://dx.doi.org/10.1016/S1474-4422(16)00017-X



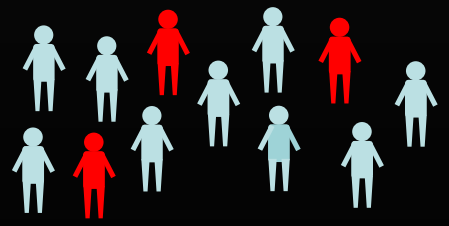
Improving precision of neuropathic pain treatment

Enhanced specificity

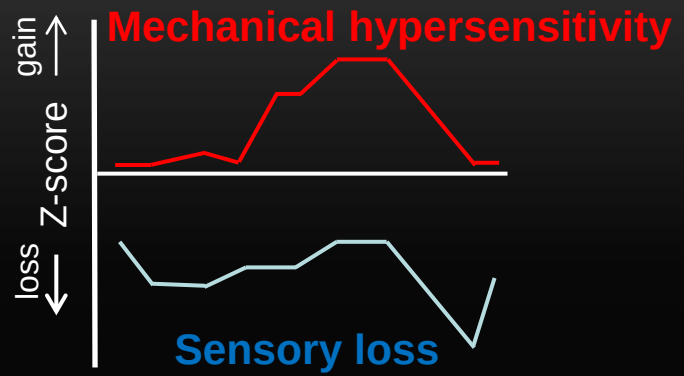
Empirical

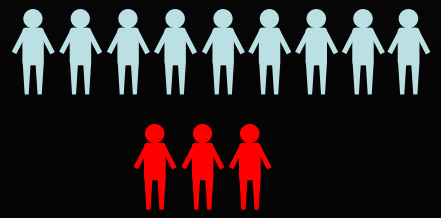
PAIN®

Systematic review of treatment of neuropathic pain.

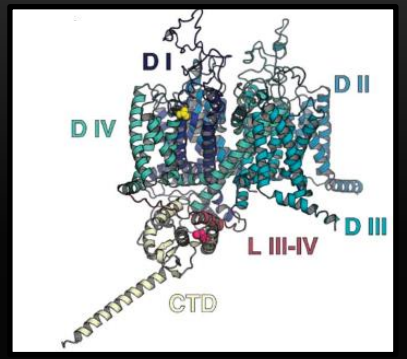


Stratified



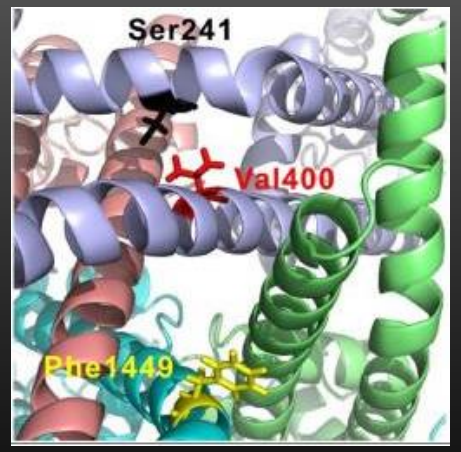


Personalised

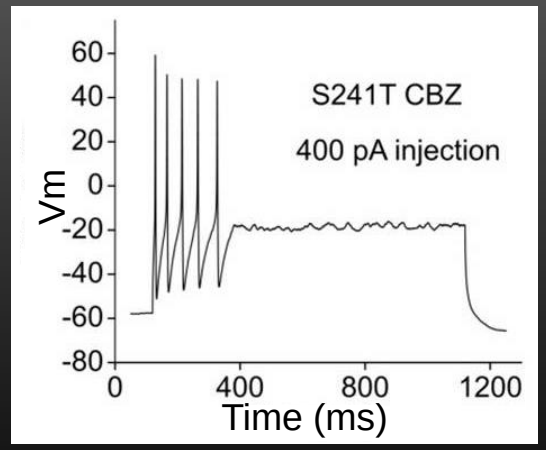


Personalised pain medicine: Predicting pharmacotherapy

Nav1.7 mutations associated with erythromelalgia V400M respond to Carbamazepine. Can this be used to predict response in other mutations? S241T is in close proximity.



Yang Y, et al.,Nat Commun. 2012



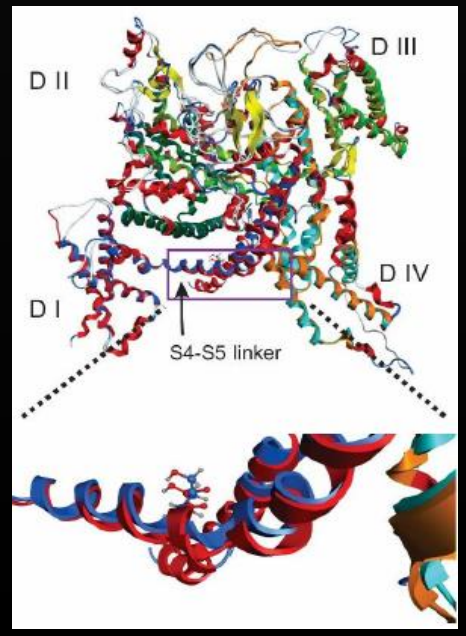
Geha et al., JAMA 2016

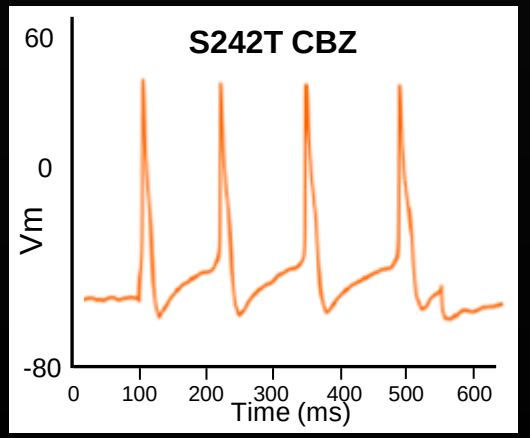
Predicting response in another ion channel: Nav1.8

Mutation in Nav1.8.

Nav1.7 (S241T)	**KTIVGALIQTVKKLSD**
Nav1.8 (S242T)	**KVIVGALIHTVKKLAD**

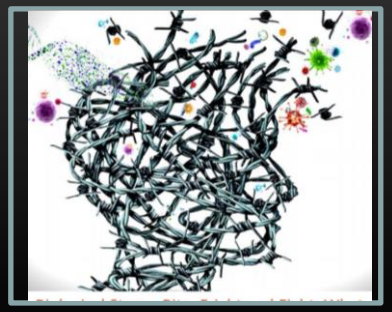
Han et al., Mol Pharm 2018





Stratification of orofacial pain patients?

Outcomes: More accurate diagnosis, prognosis and treatment choice



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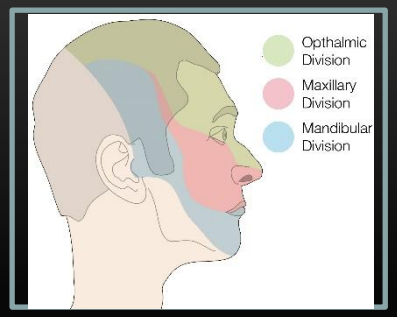

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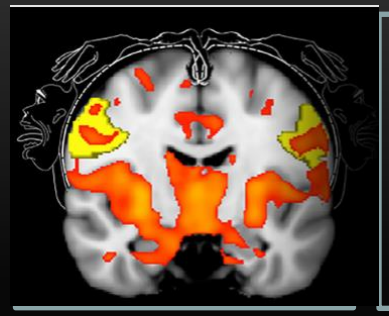

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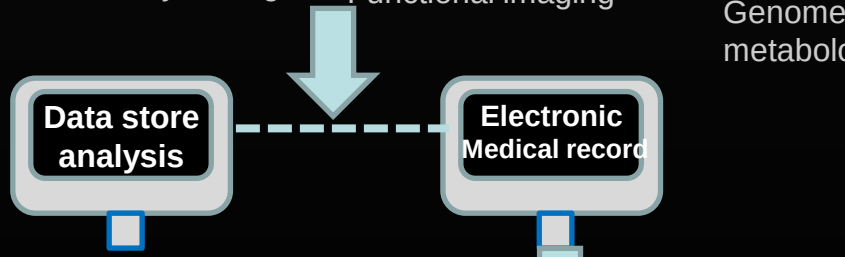
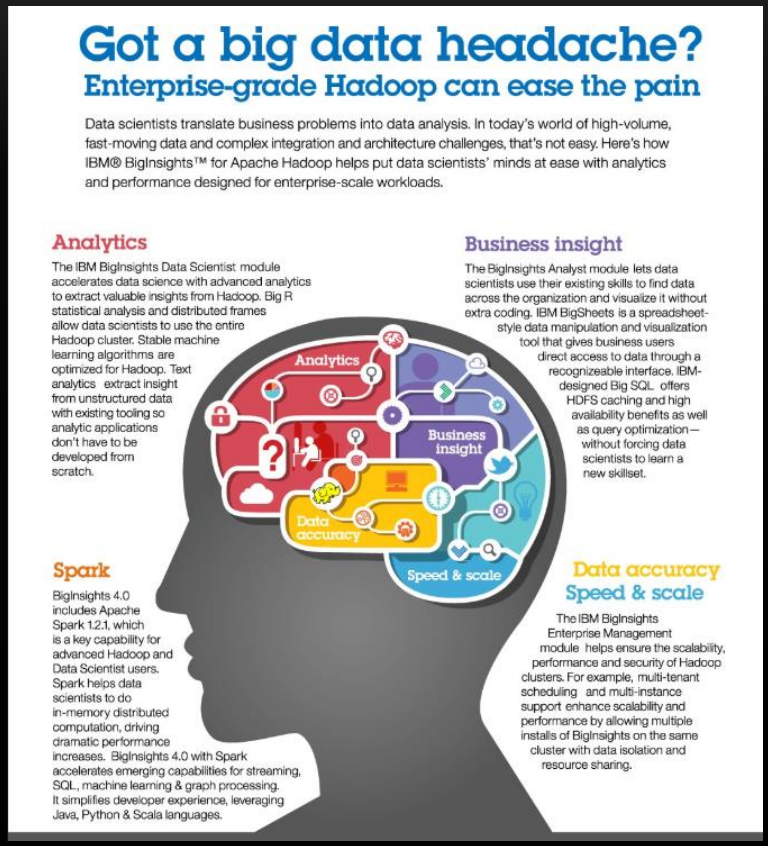
Machine learning and Ai to improve diagnosis and clustering for treatment



Prof David Bennett

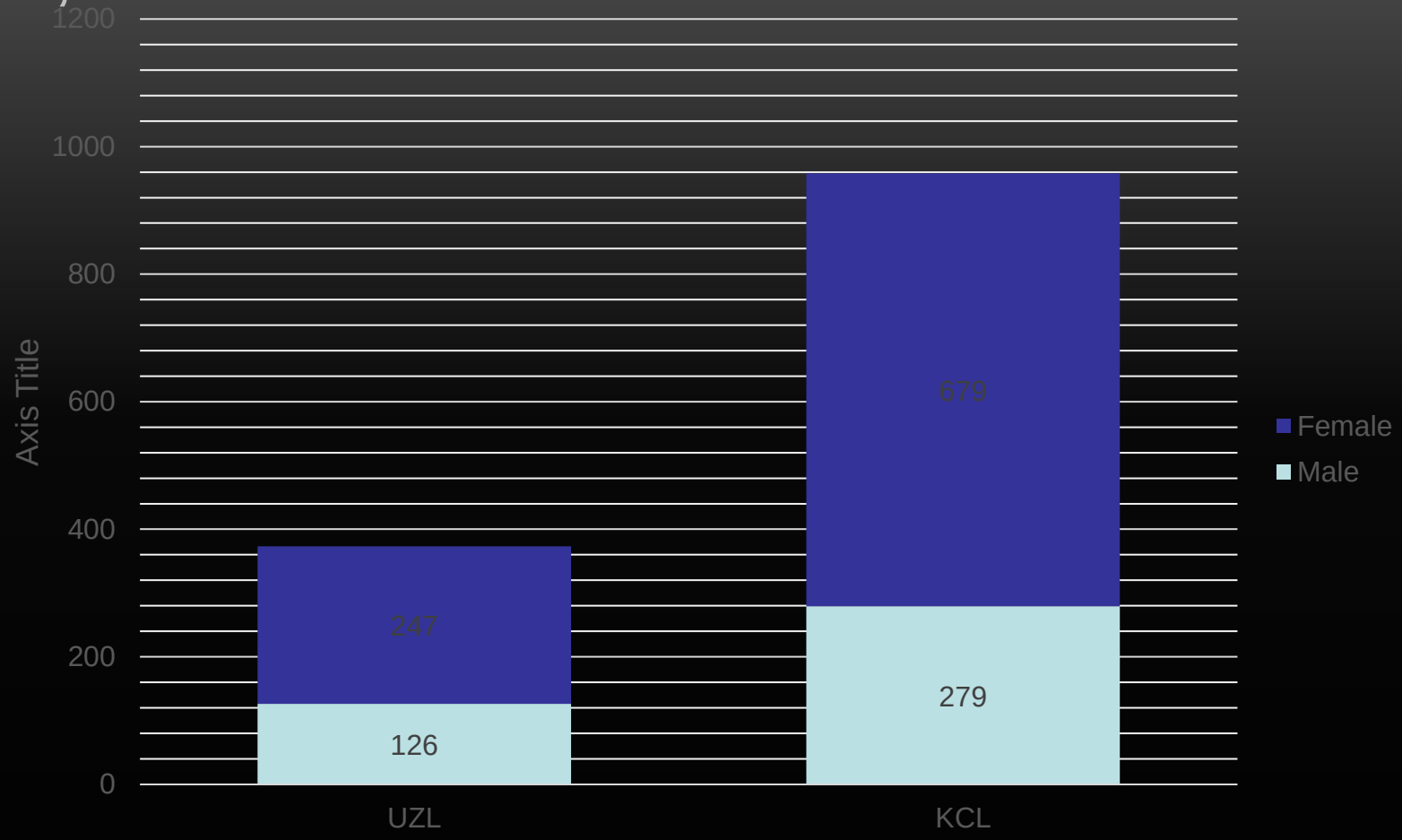
Machine learning on large patient datasets

- 1331/1500 trigeminal nerve injury patients
  - Collaboration with University of Leuven
    - Frederic Van der Cruyssen
    - Constantis Politis
    - Reinhilde Jacobs
- 600/1500 orofacial pain patients
    - Aalia Karamat MPhil student
    - Jared Smith Health psychologist



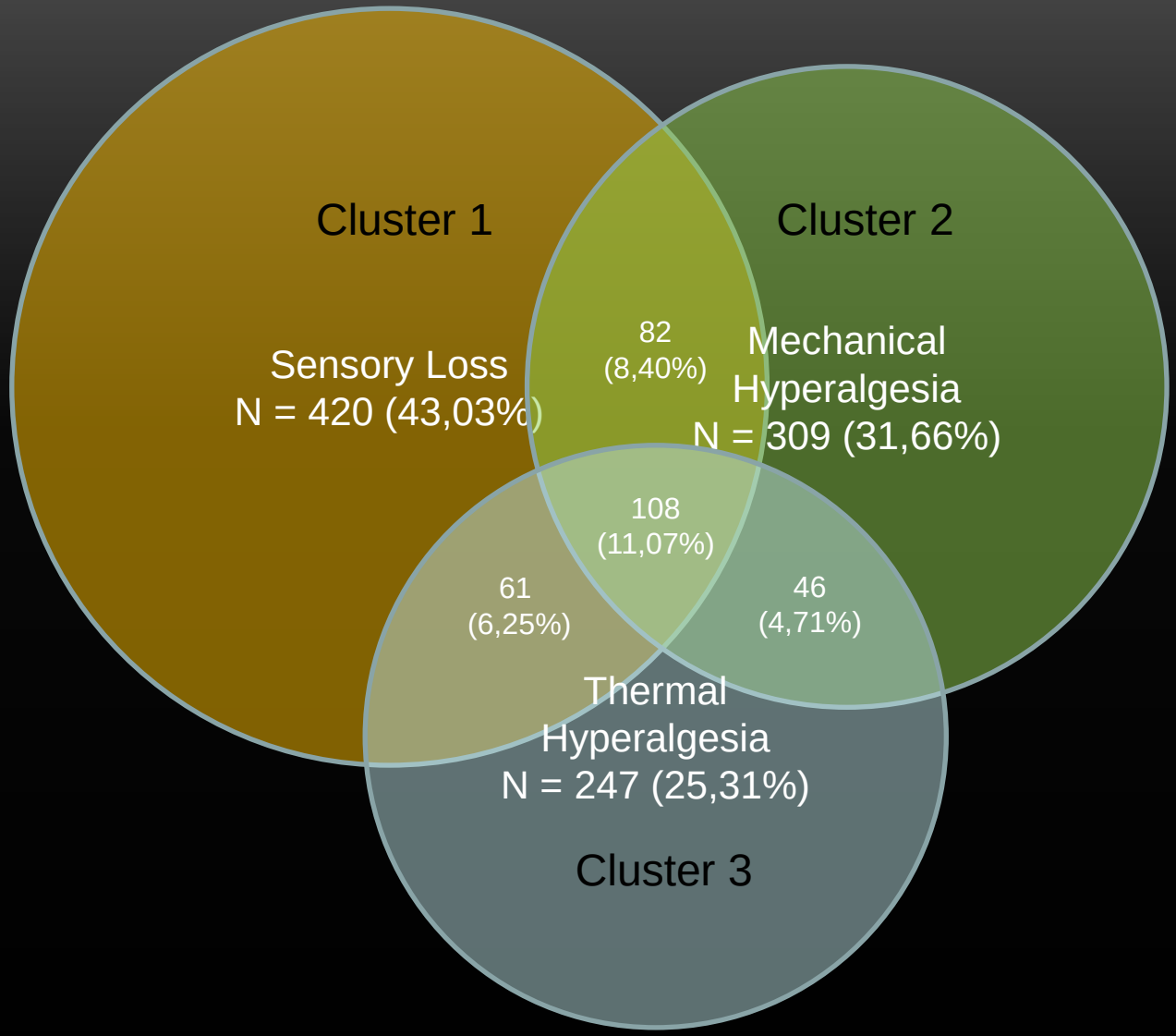
1331 Trigeminal nerve injury patients

Sample size, Male/female ratio



		UZL	KCL	Total
Male	n/N (%)	126/373 (33.78%)	279/958 (29.12%)	405/1331 (30.43%)
Female	n/N (%)	247/373 (	679/958 (	926/1331 (

Clustering of Sensory Profiles (N = 976)



Spearman Correlation Matrix Sensory Profile & Treatments

P	SL-P	SL+P	MH	TH	MH+SL+P	TH+SL+P	MH+TH	MH+TH+SL+P	
		Cluster 1	Cluster 2	Cluster 3	Cluster 1+2	Cluster 1+3	Cluster 2+3	Cluster 1+2+3	
,084	**-,129**	**-,062**	**,146**	**,079**	**,096**	,041	,034	-,017	**NSAID**
,023	**-,118**	**-,057**	**,227**	**,089**	**,098**	,036	,043	-,040	**Paracetamol**
-,012	-,013	**,051**	**,062**	-,022	**,054**	-,031	-,027	-,022	**Corticosteroids**
-,076	,000	**,205**	,008	-,007	**,086**	-,016	-,029	**-,080**	**VitaminB**
,146	**-,197**	**-,056**	**,201**	**,100**	**,069**	,027	**,069**	-,052	**TCA**
,068	**-,095**	**-,063**	**,119**	**,105**	**,077**	,003	**,056**	-,039	**Opioids**
,039	**-,069**	-,027	**,123**	,004	,035	,008	,045	-,015	**SSRI**
,233	**-,193**	**-,079**	**,152**	**,061**	,029	-,005	,080	-,043	**Anti-epileptics**
,110	**-,125**	**-,077**	**,277**	,009	,027	-,034	,032	-,030	**Benzodiazepines**
,051	**-,064**	-,008	,042	,004	,087	,040	,008	-,024	**Antibiotics**
,083	**-,062**	-,034	**,061**	-,018	,027	,007	,015	-,009	**Capsaicin**
,025	-,037	-,031	,033	**,063**	,076	-,015	-,013	-,020	**LidocainPatch**
-,018	,002	,010	-,010	-,003	,002	**,133**	-,036	,003	**CBT**

Box/number in bold: $P < 0.05$

A negative value means negative correlated
A positive value means positive correlated
A value of zero means no correlation

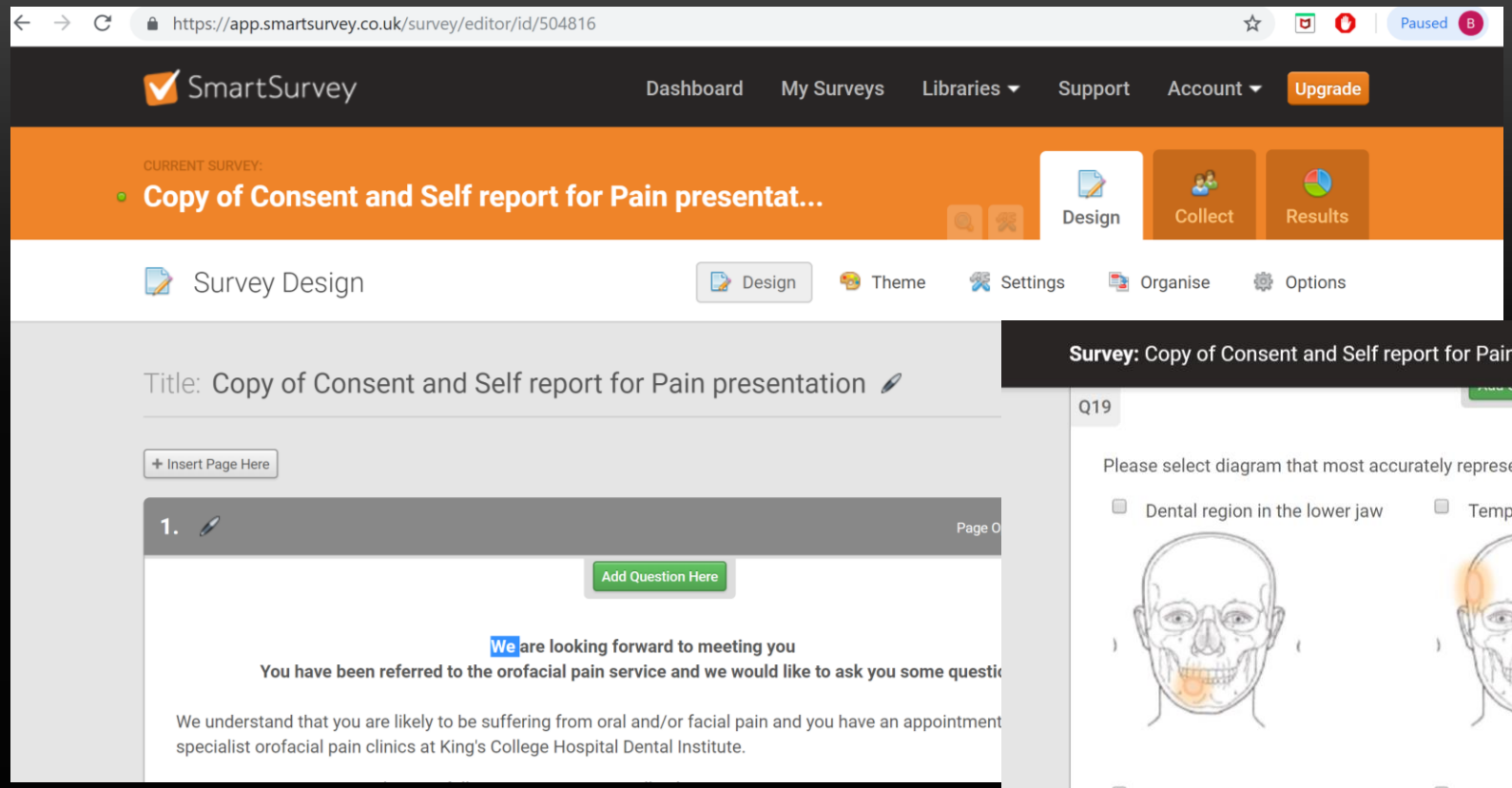
0,00-0,19: very weak correlation
0,20-0,39: weak
0,40-0,59: moderate
0,60-0,79: strong
0,80-1,00: very strong

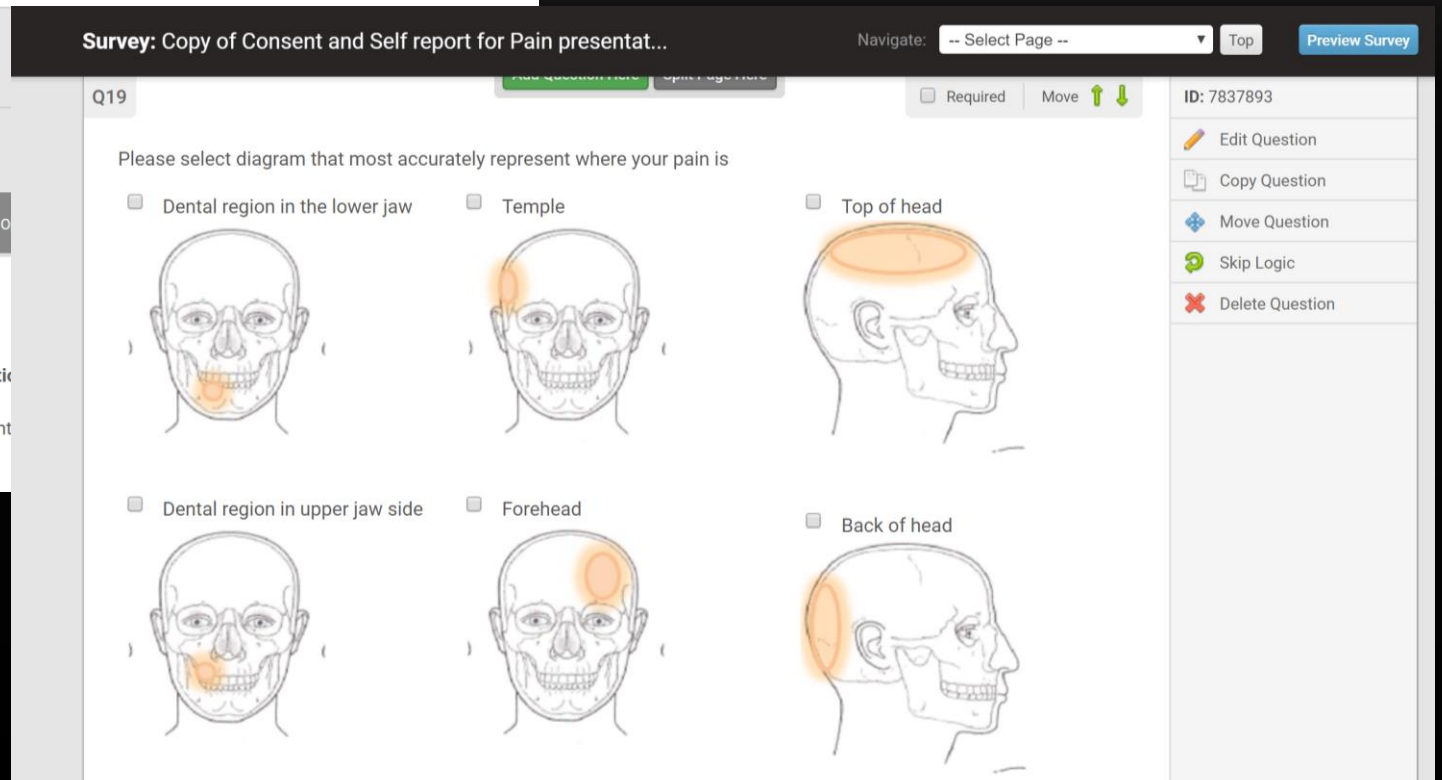
P: pain, SL: sensory loss, MH: mechanical hyperalgesia, TH: thermal hyperalgesia

Prediction Model RapidMiner (generalized linear model)

Agreed national core data for OFP history Axis 1 and Axis 2

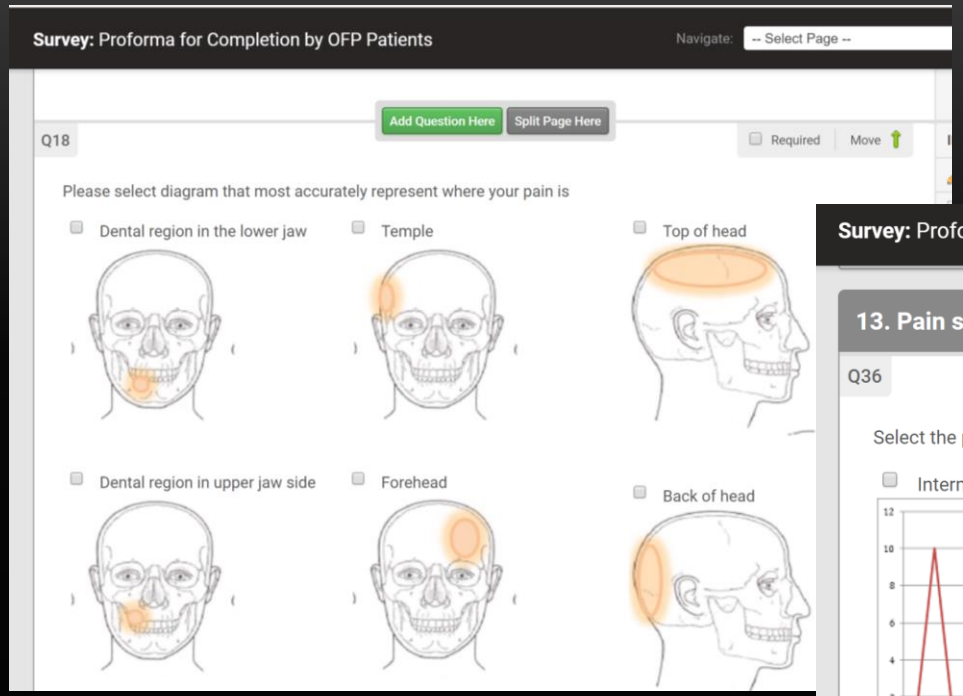
- Prof Justin Durham
- Prof Joanna Zakrzewska

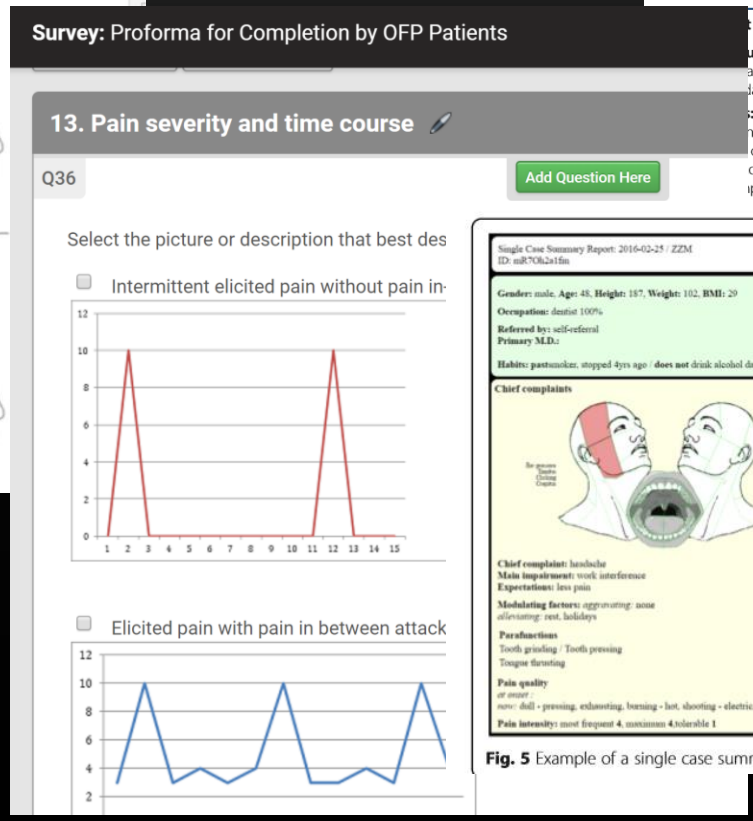




Online questionnaires-dashboard collaboration (inform)

Big Data/ Machine learning/ Diagnostic app development






Ettlin *et al. The Journal of Headache and Pain* (2016) 17:77
DOI 10.1186/s10194-016-0670-5

The Journal of Headache and Pain

METHODOLOGY Open Access

Design, construction, and technical implementation of a web-based interdisciplinary symptom evaluation (WISE) - a heuristic proposal for orofacial pain and temporomandibular disorders

Dominik A. Ettlin[1], Isabelle Sommer[1], Ben Brönnimann[1], Sergio Maffioletti[2], Jörg Scheidt[3], Mei-Yin Hou[1], Nenad Lukic[1] and Beat Steiger[1*]

Background: Medical symptoms independent of body location burden individuals to varying degrees and may are by more than one expert. Various paper and computer-based tools exist that aim to comprehensively data for optimal clinical management and research.

Methods: A web-based interdisciplinary symptom evaluation (WISE) was newly designed, constructed, and technically nted. For worldwide applicability and to avoid copyright infringements, open source software tools and free questionnaires available in multiple languages were used. Highly secure data storage limits access strictly to o use the tool for collecting, storing, and evaluating their data. Concept and implementation is illustrated by a ple tailored for the requirements of a single center in Switzerland providing interdisciplinary care to orofacial

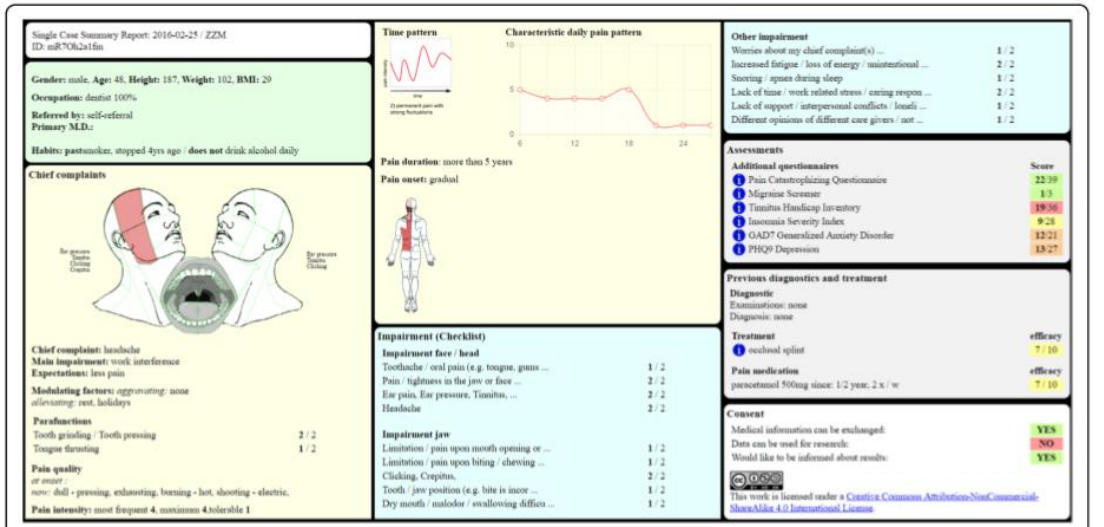


Fig. 5 Example of a single case summary report

Orofacialpain.org.uk

Stimulation

Sphenopalatine ganglion (SPG) stimulation for cluster headaches

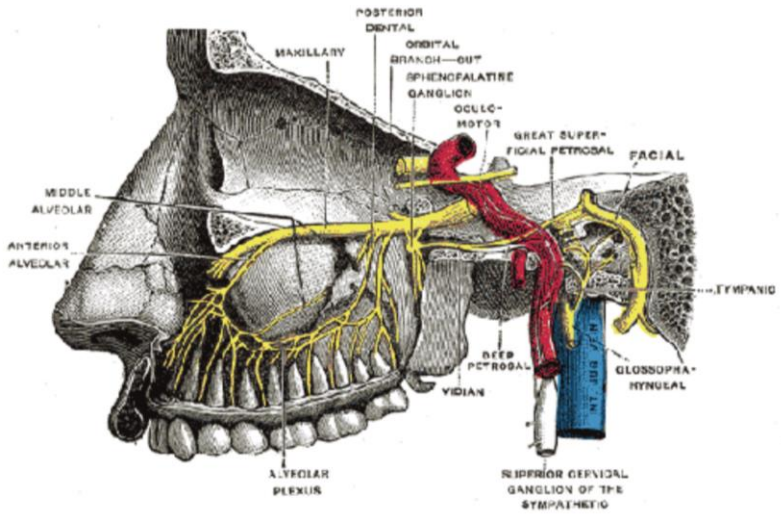
80% of Autonomic Nervous system ANS fibers are thought to be sensory in nature and may be directly involved in **pain perception**.

Sensory autonomic nerves are present in the cranial membranes (dura, arachnoid, tentorium), in the connective tissue and in the walls of the larger blood and lymphatic vessels.

The ANS is known to have a wind-up effect (sensitizing effect) on the wide dynamic range(WDR) cells in the spinal chord, which modulate the pain pathway. If pain originates for example in the trigeminal system, this message has to pass through the WDR cells.

In Europe, a multicenter clinical trial from 2010 – 2013, the Pathway CH-1 study, showed an overall reduction in disability from cluster headache in participants who used a handheld controller to activate an implanted SPG neurostimulator at the start of a headache attack. Of the 32 participants, 68% had a reduction in pain during the attack of at least 50%, had at least 50% fewer attacks, or both. (2)

A subsequent U.S. clinical trial, Pathway CH-2, was expected to be completed in January 2017.

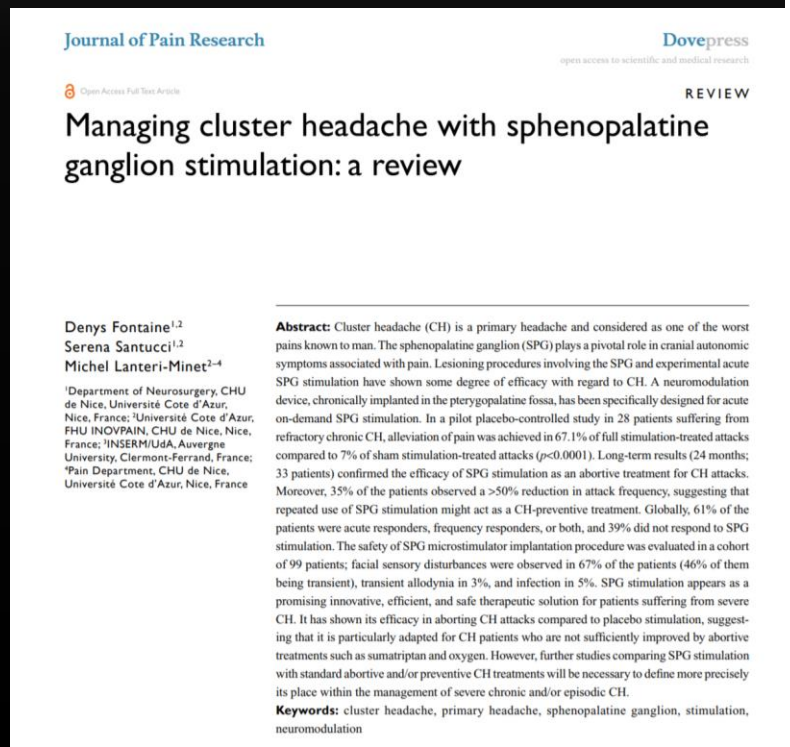


The SPG is connected to a complex neural pathway involved in headache that is associated with the

Schoenen J, Jensen RH, Lantéri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: A randomized, sham-controlled study. *Cephalalgia*. 2013;33(10):816-830.
Pietzsch JB, Garner A, Gaul C, May A. Cost-effectiveness of stimulation of the sphenopalatine ganglion (SPG) for the treatment of chronic cluster headache: a model-based analysis based on the Pathway CH-1 study. *The Journal of Headache and Pain*. 2015;16:48. doi:10.1186/s10194-015-0530-8. doi:10.1177/0333102412473667.

Sphenopalatine ganglion (SPG) stimulation for cluster headaches

- Peter Goadsby and team at KCL Kings College Hospital
  - N=6 patients
- Prof Adnan Al Kaisi, Dr Giorgio Lambru and team at Input pain management at St Thomas Hospital
  - N= 4 patients
  - Migraine?



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REVIEW

Managing cluster headache with sphenopalatine ganglion stimulation: a review

Denys Fontaine[1,2]
Serena Santucci[1,2]
Michel Lanteri-Minet[2–4]

[1]Department of Neurosurgery, CHU de Nice, Université Cote d'Azur, Nice, France; [2]Université Cote d'Azur, FHU INOVPAIN, CHU de Nice, Nice, France; [3]INSERM/UdA, Auvergne University, Clermont-Ferrand, France; [4]Pain Department, CHU de Nice, Université Cote d'Azur, Nice, France

Abstract: Cluster headache (CH) is a primary headache and considered as one of the worst pains known to man. The sphenopalatine ganglion (SPG) plays a pivotal role in cranial autonomic symptoms associated with pain. Lesioning procedures involving the SPG and experimental acute SPG stimulation have shown some degree of efficacy with regard to CH. A neuromodulation device, chronically implanted in the pterygopalatine fossa, has been specifically designed for acute on-demand SPG stimulation. In a pilot placebo-controlled study in 28 patients suffering from refractory chronic CH, alleviation of pain was achieved in 67.1% of full stimulation-treated attacks compared to 7% of sham stimulation-treated attacks ($p<0.0001$). Long-term results (24 months; 33 patients) confirmed the efficacy of SPG stimulation as an abortive treatment for CH attacks. Moreover, 35% of the patients observed a >50% reduction in attack frequency, suggesting that repeated use of SPG stimulation might act as a CH-preventive treatment. Globally, 61% of the patients were acute responders, frequency responders, or both, and 39% did not respond to SPG stimulation. The safety of SPG microstimulator implantation procedure was evaluated in a cohort of 99 patients; facial sensory disturbances were observed in 67% of the patients (46% of them being transient), transient allodynia in 3%, and infection in 5%. SPG stimulation appears as a promising innovative, efficient, and safe therapeutic solution for patients suffering from severe CH. It has shown its efficacy in aborting CH attacks compared to placebo stimulation, suggesting that it is particularly adapted for CH patients who are not sufficiently improved by abortive treatments such as sumatriptan and oxygen. However, further studies comparing SPG stimulation with standard abortive and/or preventive CH treatments will be necessary to define more precisely its place within the management of severe chronic and/or episodic CH.

Keywords: cluster headache, primary headache, sphenopalatine ganglion, stimulation, neuromodulation

Barloese *et al. The Journal of Headache and Pain* (2018) 19:6
DOI 10.1186/s10194-017-0828-9

The Journal of Headache and Pain

RESEARCH ARTICLE Open Access

CrossMark

Sphenopalatine ganglion stimulation for cluster headache, results from a large, open-label European registry

Mads Barloese[1,2*], Anja Petersen[2], Philipp Stude[3], Tim Jürgens[4], Rigmor Højland Jensen[2] and Arne May[5]

Abstract

Background: Cluster headache (CH) is a disabling primary headache disorder characterized by severe periorbital pain. A subset of patients does not respond to established pharmacological therapy. This study examines outcomes of a cohort of mainly chronic CH patients treated with sphenopalatine ganglion (SPG) stimulation.

Methods: Patients were followed in an open-label prospective study for 12 months. Ninety-seven CH patients (88 chronic, 9 episodic) underwent trans-oral insertion of a microstimulator targeting the SPG. Patients recorded stimulation effect prospectively for individual attacks. Frequency, use of preventive and acute medications, headache impact (HIT-6) and quality of life measures (SF-36v2) were monitored at clinic visits. Per protocol, frequency responders experienced ≥50% reduction in attack frequency and acute responders treated ≥50% of attacks. HIT-6 responders experienced an improvement ≥2.3 units and SF-36 responders ≥ 4 units vs. baseline.

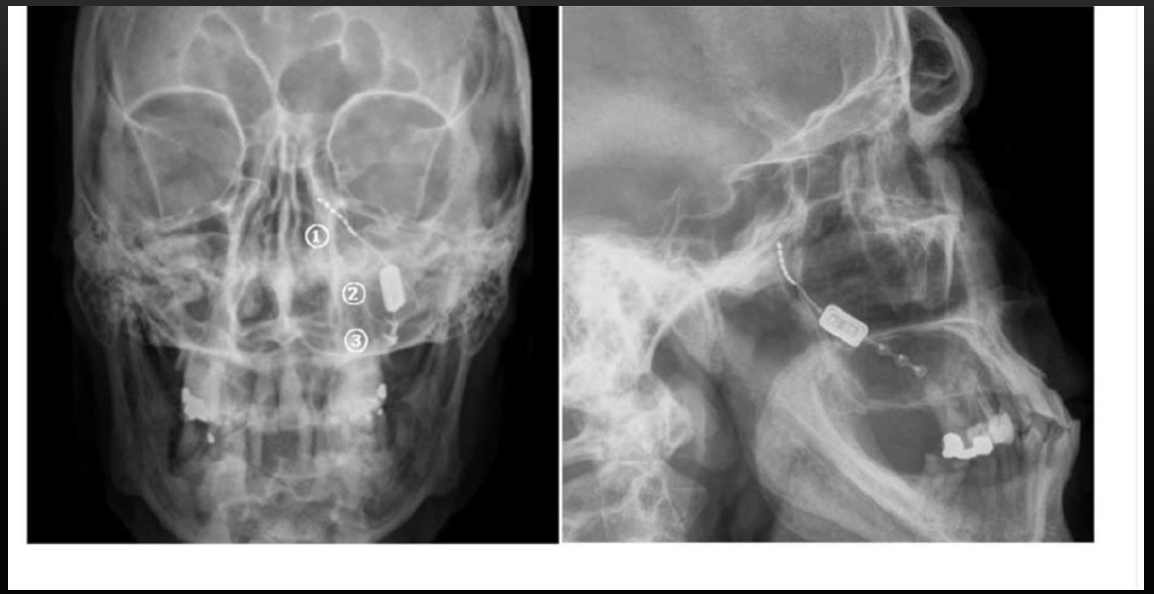
Results: Eighty-five patients (78 chronic, 7 episodic) remained implanted and were evaluated for effectiveness at 12 months. In total, 68% of all patients were responders, 55% of chronic patients were frequency responders and 32% of all patients were acute responders. 67% of patients using acute treatments were able to reduce the use of these by 52% and 74% of chronic patients were able to stop, reduce or remain off all preventive medications. 59% of all patients were HIT-6 responders, 67% were SF-36 responders.

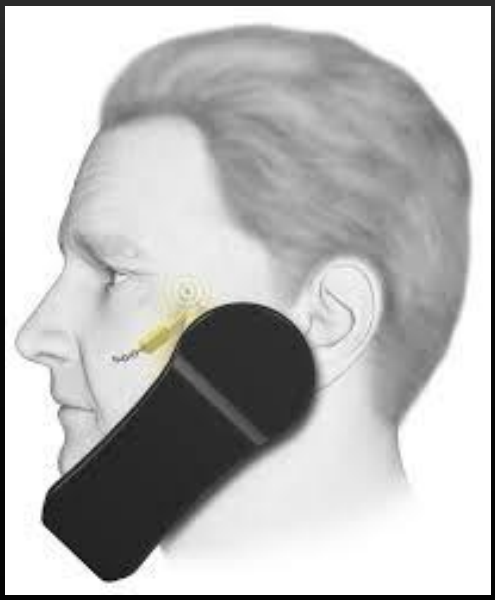
Conclusions: This open-label registry corroborates that SPG stimulation is an effective therapy for CH patients providing therapeutic benefits and improvements in use of medication as well as headache impact and quality of life.

Keywords: Cluster headache, Sphenopalatine ganglion, Neurostimulation, Neuromodulation, Long term effectiveness

Sphenopalatine ganglion (SPG) stimulation for cluster headaches

Using an intraoral approach to place neurostimulator for reducing frequency, duration and intensity of pain attacks





Tara Renton one of 4 surgeons in UK trained for placing this device

Other strategies for OFP

Botulinum Toxin A

Burmeister *et al. Trials* (2015) 16:550
DOI 10.1186/s13063-015-1052-z

TRIALS

STUDY PROTOCOL Open Access

Botulinum neurotoxin type A in the treatment of classical Trigeminal Neuralgia (BoTN): study protocol for a randomized controlled trial

Jan Burmeister[1*], Dagny Holle[1], Eva Bock[2], Claudia Ose[2], Hans-Christoph Diener[1] and Mark Obermann[1]

Abstract

Background: Trigeminal neuralgia is characterized by paroxysmal facial pain attacks. Adequate prophylactic drug therapy is often limited by the lack of efficacy and intolerance due to central nervous system side effects. Subcutaneous injections of botulinum toxin type A are a promising treatment option for patients with unsatisfactory response to drug therapy or neurosurgical intervention. Its effects are expected to last for at least 3 months, so it could be a potential long-term treatment.
This is the study protocol of a prospective, placebo-controlled, double blind clinical trial investigating the add-on therapy of subcutaneous administration of botulinum toxin type A injections to standard treatment in therapy-refractory classical trigeminal neuralgia.

Methods and design: BoTN is a prospective, double blind, placebo-controlled trial with a randomized withdrawal design in which a single blind phase is followed by a double blind phase (see also Methods and design). Eligible patients with classical trigeminal neuralgia who are otherwise refractory to medical and neurosurgical treatment will receive subcutaneous injections of botulinum toxin type A into injection sites of the affected trigeminal branch. In the first phase all patients will receive botulinum toxin type A in a single blinded intervention. Twelve weeks later therapy responders will be allocated to the *verum* or placebo (saline) arm in a double blind, randomized manner. These injections will be performed at the same sites as the first injections.
This trial will be conducted in a tertiary outpatient clinic specialized in the treatment of headache and facial pain. There will be three investigators performing the injections who are experienced in the treatment of headache and facial pain and trained in botulinum toxin type A injections.

Discussion: BoTN is designed to assess the efficacy and safety of subcutaneous botulinum toxin type A injections in addition to standard prophylactic treatment in therapy-refractory trigeminal neuralgia.

Trial registration number: EU Clinical Trials Register: EudraCT-No: 2014-001959-24 https://www.clinicaltrials register.eu/ctr-search/rest/download/trial/2014-001959-24/DE
Date of trial registration
26 August 2014

Keywords: Trigeminal neuralgia, Botulinum toxin type A, Prophylactic treatment, Clinical trial, Prospective study, Study protocol

Vol. 122 No. 1 July 2016

The efficacy of botulinum toxin for the treatment of trigeminal and postherpetic neuralgia: a systematic review with meta-analyses

Thomas Shackleton, DDS, MS,[a] Saravanan Ram, DDS, MS,[b] Misty Black, DDS, MS,[a] Jon Ryder, DDS, MS,[a] Glenn T. Clark, DDS, MS,[c] and Reyes Enciso, PhD[d]

Objective. To evaluate the efficacy of a botulinum toxin type A (BoTN-A) in treating trigeminal neuralgia (TN) and postherpetic neuralgia (PHN).
Study Design. Three databases were searched: Medline, Web of Science, and Cochrane Library. The search was restricted to English-language randomized, placebo-controlled trials. Three review authors evaluated the cases for risk of bias.
Results. Six studies were eligible for inclusion. Pooled results showed a difference in post-treatment pain intensity of −3.009 (95% confidence interval −4.566 to −1.453; $P < .001$) in favor of BoTN-A compared with placebo in managing TN or PHN. Of the six studies, five had unclear risk of bias, and one showed high risk.
Conclusions. Although the studies had unclear or high risk of bias, moderate evidence regarding the efficacy of BoTN-A in treating TN and PHN was found. BoTN-A might be an alternative treatment to those patients who are either unable to manage their pain medically or would like adjunct therapy. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:61-71)

Neuralgia is described as pain extending along the course of one or more nerves. Many varieties of neuralgia are distinguished according to the nerves affected, such as the trigeminal, brachial, occipital, and supraorbital nerves, or to the cause, such as postherpetic, anemic, diabetic, gouty, malarial, or syphilitic factors.[1] Pain from neuralgias is often debilitating to those who suffer from it. These patients often suffer for extended periods before any sort of beneficial therapy is suggested.[2] There are two major treatment strategies for neuralgias: pharmacotherapy and neurosurgery. Medical management is the mainstay treatment for most neuralgias, since it generally carries a lower risk compared with major surgical procedures and is suitable for medically compromised patients who are unfit for such surgery.[3] However, side effects from systemic medications, such as ataxia, dizziness, nausea, fatigue, rash, and somnolence, can be problematic and debilitating.

Botulinum toxin type A (BoTN-A) is a potent neurotoxin that blocks acetylcholine release from presynaptic nerve endings by interfering with the activity of SNARE (soluble *N*-ethylamide-sensitive-factor attachment protein receptors) proteins. BoTN-A has been reported to have analgesic effects independent of its action on muscle tone.[4] The most significant results have been observed in patients with neuropathic pain. Neuropathic pain caused by peripheral lesions has been the most widely studied. BoTN-A has shown its efficacy on pain and allodynia in various animal models of inflammatory neuropathic pain.[4] The objective of this review was to determine the efficacy of BoTN-A when used as a treatment in patients suffering from trigeminal neuralgia (TN) or postherpetic neuralgia (PHN).

MATERIALS AND METHODS

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[5]

Eligibility criteria

Studies were limited to randomized controlled trials (RCTs) on the efficacy of BoTN-A compared with

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[b]Associate Professor of Clinical Dentistry, Program Director, Oral Medicine, Herman Ostrow School of Dentistry of USC, Los Angeles, CA, USA.
[c]Professor of Dentistry, Program Director, Orofacial Pain, Herman Ostrow School of Dentistry of USC, Los Angeles, CA, USA.
[d]Associate Professor of Clinical Dentistry, Herman Ostrow School of Dentistry of USC, Los Angeles, CA, USA.
Received for publication Oct 10, 2015; returned for revision Jan 4, 2016; accepted for publication Mar 4, 2016.

2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2016.03.003

Statement of Clinical Relevance

In this systematic review, the number of eligible studies was small, and the authors found unclear or high risk of bias in the included studies. However, moderate evidence regarding the efficacy of botulinum toxin A in treating trigeminal and postherpetic neuralgia was found; this evidence provides hope that this may be an alternative treatment for those patients who are either unable to manage their pain medically or would like an adjunct therapy.

Morra *et al. The Journal of Headache and Pain* (2016) 17:63
DOI 10.1186/s10194-016-0651-8

The Journal of Headach and Pa

REVIEW ARTICLE Open Acces

Therapeutic efficacy and safety of *Botulinum Toxin A Therapy* in *Trigeminal Neuralgia*: a systematic review and meta-analysis of randomized controlled trials

Mostafa Ebraheem Morra[1†], Ahmed Elgebaly[1†], Ahmed Elmaraezy[1†], Adham M. Khalil[2†], Ahmed M. A. Altibi[3], Tran Le-Huy Vu[4], Mostafa Reda Mostafa[5], Nguyen Tien Huy[6,7*] and Kenji Hirayama[8*]

Abstract

Background: Several different interventions have been examined to alleviate pain and reduce frequency of trigeminal neuralgia (TN) paroxysms. However, some patients continue to have persistent or recurrent painful attacks. Using a systematic review and meta-analysis approach, we aimed to synthesize evidence from published randomized controlled trials (RCTs) regarding safety and efficacy of botulinum toxin type A (BTX-A) as a possible emerging choice of treatment for TN.

Methods: We conducted an electronic search in 10 databases/electronic search engines to access relevant publications. All articles in all languages reporting RCTs on the efficacy and safety of BTX-A in the treatment of TN were included for systematic review and meta-analysis.

Results: A total of four RCTs (n = 178) were identified for final meta-analysis. The overall effect favored BTX-A versus placebo in terms of proportion of responders (risk ratio RR = 2.87, 95 % confidence interval CI [1.76, 4.69], p <0.0001 with no significant detected heterogeneity (p = 0.31; I^2 = 4 %). Paroxysms frequency per day was significantly lower for BTX-A group (mean difference MD = -29.79, 95 % CI [-38.50,–21.08], p <0.00001) with no significant heterogeneity (p = 0.21; I^2 = 36 %).

Conclusion: Despite limited data, our results suggest that BTX-A may be an effective and safe treatment option for patients with TN. Further larger and well-designed RCTs are encouraged to translate these findings into better clinical outcome and better quality of life for TN patients.

Keywords: Botulinum, BTX-A, Trigeminal neuralgia, Clinical trials, Systematic review, Meta-analysis

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Pre Botox LA injections for focal neuropathic pain

Lidocaine 2% (1:80K epinephrine) 1-2mls infiltrations
positive response prerequisite for BTX treatment but not predictive

PDAP 1 or primary localised intra oral Ne Pain

- 7 patients
- Mean age 55yrs
- 60% Female
- Site
  - 40% mandibular posterior molar region
  - 40% posterior maxillary molar region
  - 20% anterior maxilla

- Response rate
  - Complete 3 (1 hour-30days)
  - Partial 2
  - None 2

PPTTN localised intra oral Ne Pain

- 18 patients
- Mean age 42 yrs
- 75% female
- Site
  - 15% mandibular posterior molar region
  - 5% posterior maxillary molar region
  - 80% anterior maxilla
- Response rate
  - Complete 14 (duration 1 hour -42 days)
  - Partial 2
  - None 2

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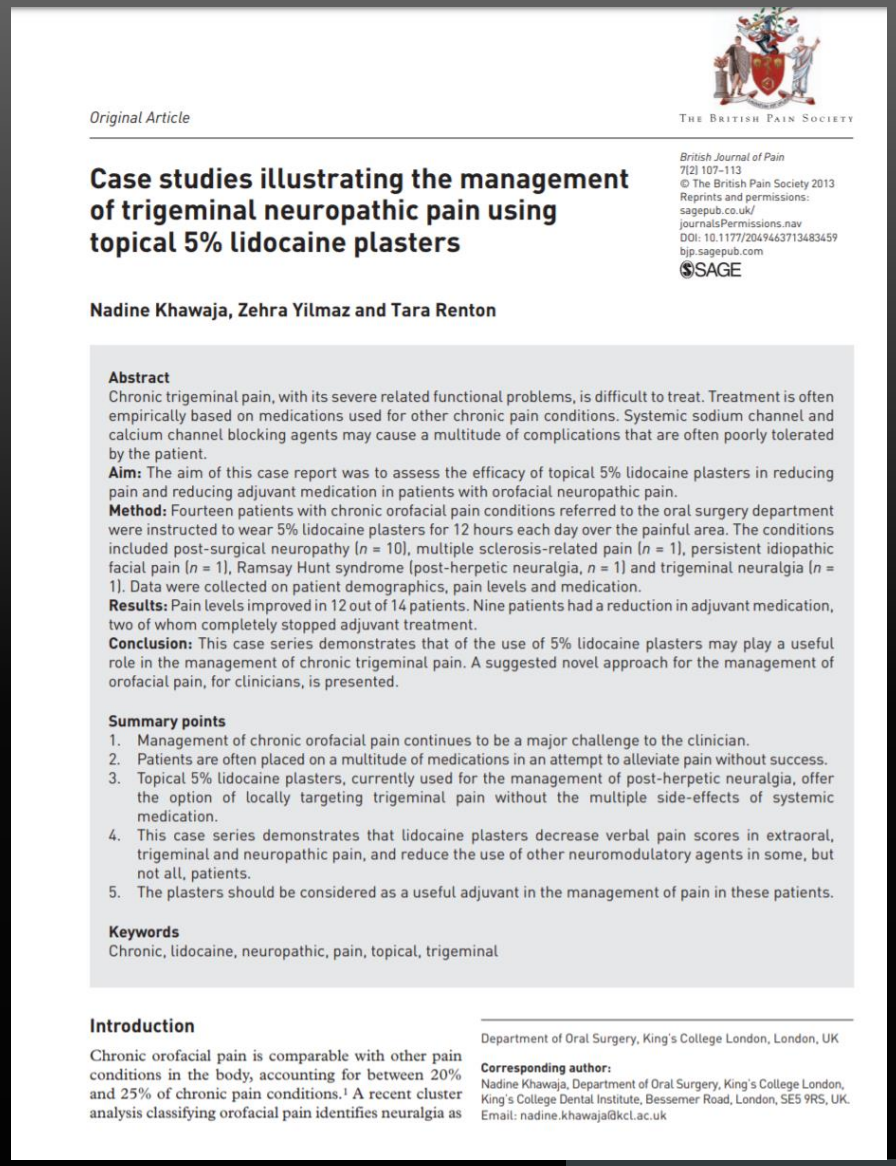
Medical Management- topical 5% Lidocaine Versatis patches

- Excellent in minimising elicited pain due to:
- Cold allodynia caused by sport and winter activity
- Mechanical allodynia interfering sleep



Original Article

THE BRITISH PAIN SOCIETY

British Journal of Pain
7(2) 107–113

DOI: 10.1177/2049463713483459
bjp.sagepub.com
SAGE

Case studies illustrating the management of trigeminal neuropathic pain using topical 5% lidocaine plasters

Nadine Khawaja, Zehra Yilmaz and Tara Renton

Abstract

Chronic trigeminal pain, with its severe related functional problems, is difficult to treat. Treatment is often empirically based on medications used for other chronic pain conditions. Systemic sodium channel and calcium channel blocking agents may cause a multitude of complications that are often poorly tolerated by the patient.

Aim: The aim of this case report was to assess the efficacy of topical 5% lidocaine plasters in reducing pain and reducing adjuvant medication in patients with orofacial neuropathic pain.

Method: Fourteen patients with chronic orofacial pain conditions referred to the oral surgery department were instructed to wear 5% lidocaine plasters for 12 hours each day over the painful area. The conditions included post-surgical neuropathy (n = 10), multiple sclerosis-related pain (n = 1), persistent idiopathic facial pain (n = 1), Ramsay Hunt syndrome (post-herpetic neuralgia, n = 1) and trigeminal neuralgia (n = 1). Data were collected on patient demographics, pain levels and medication.

Results: Pain levels improved in 12 out of 14 patients. Nine patients had a reduction in adjuvant medication, two of whom completely stopped adjuvant treatment.

Conclusion: This case series demonstrates that of the use of 5% lidocaine plasters may play a useful role in the management of chronic trigeminal pain. A suggested novel approach for the management of orofacial pain, for clinicians, is presented.

Summary points

1. Management of chronic orofacial pain continues to be a major challenge to the clinician.
2. Patients are often placed on a multitude of medications in an attempt to alleviate pain without success.
3. Topical 5% lidocaine plasters, currently used for the management of post-herpetic neuralgia, offer the option of locally targeting trigeminal pain without the multiple side-effects of systemic medication.
4. This case series demonstrates that lidocaine plasters decrease verbal pain scores in extraoral, trigeminal and neuropathic pain, and reduce the use of other neuromodulatory agents in some, but not all, patients.
5. The plasters should be considered as a useful adjuvant in the management of pain in these patients.

Keywords
Chronic, lidocaine, neuropathic, pain, topical, trigeminal

Introduction

Chronic orofacial pain is comparable with other pain conditions in the body, accounting for between 20% and 25% of chronic pain conditions.[1] A recent cluster analysis classifying orofacial pain identifies neuralgia as

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Email: nadine.khawaja@kcl.ac.uk

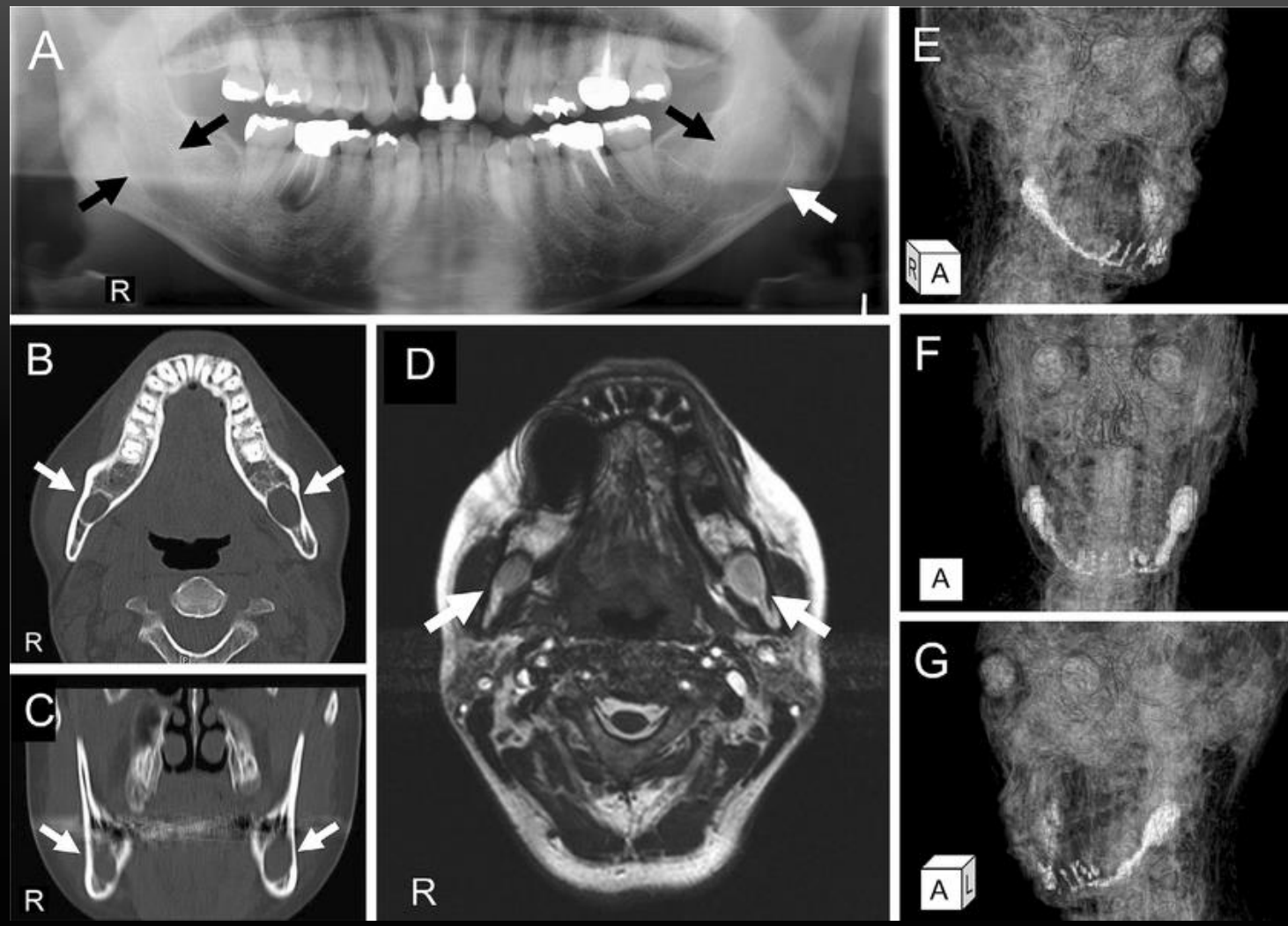
KING'S College LONDON

New developments

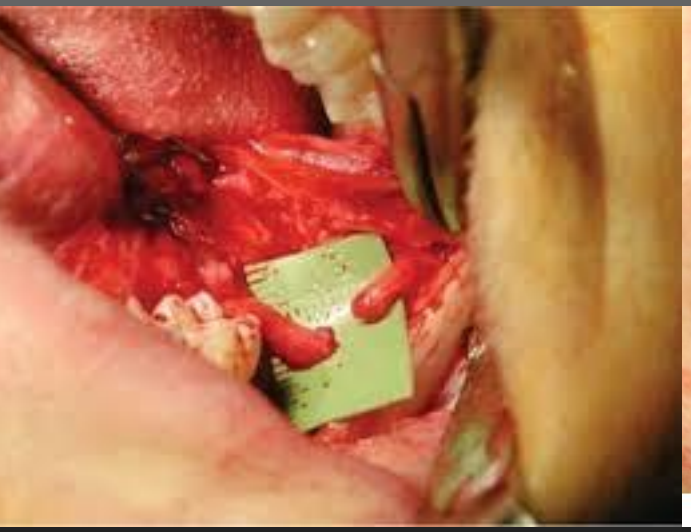
Zuniga JR, Mistry C, Tikhonov I, Dessouky R, **Chhabra** A Magnetic Resonance Neurography of Traumatic and Nontraumatic Peripheral Trigeminal Neuropathies. J Oral Maxillofac Surg. 2018 Apr;76(4):725-736. doi: 10.1016/j.joms.2017.11.007. Epub 2017 Nov 16.

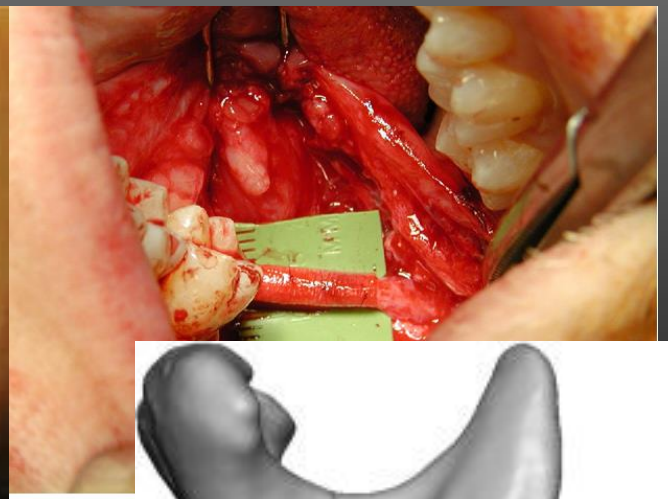
Dessouky R, Xi Y, **Zuniga J**, **Chhabra** A. Role of MR Neurography for the Diagnosis of Peripheral Trigeminal Nerve Injuries in Patients with Prior Molar Tooth Extraction. AJNR Am J Neuroradiol. 2018 Jan;39(1):162-169.

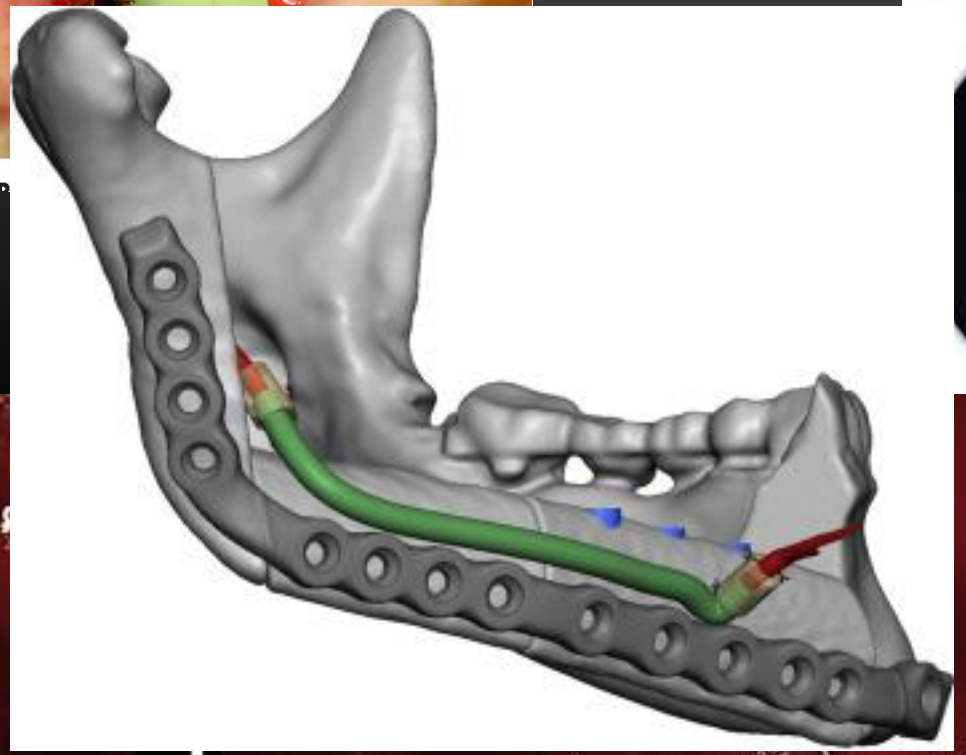
Cox B, Zuniga JR, Panchal N, Cheng J, **Chhabra** A. Magnetic resonance neurography in the management of peripheral trigeminal neuropathy: experience in a tertiary care centre. Eur Radiol. 2016 Oct;26(10):3392-400. doi: 10.1007/s00330-015-4182-5. Epub 2016 Jan 21



John Zuniga





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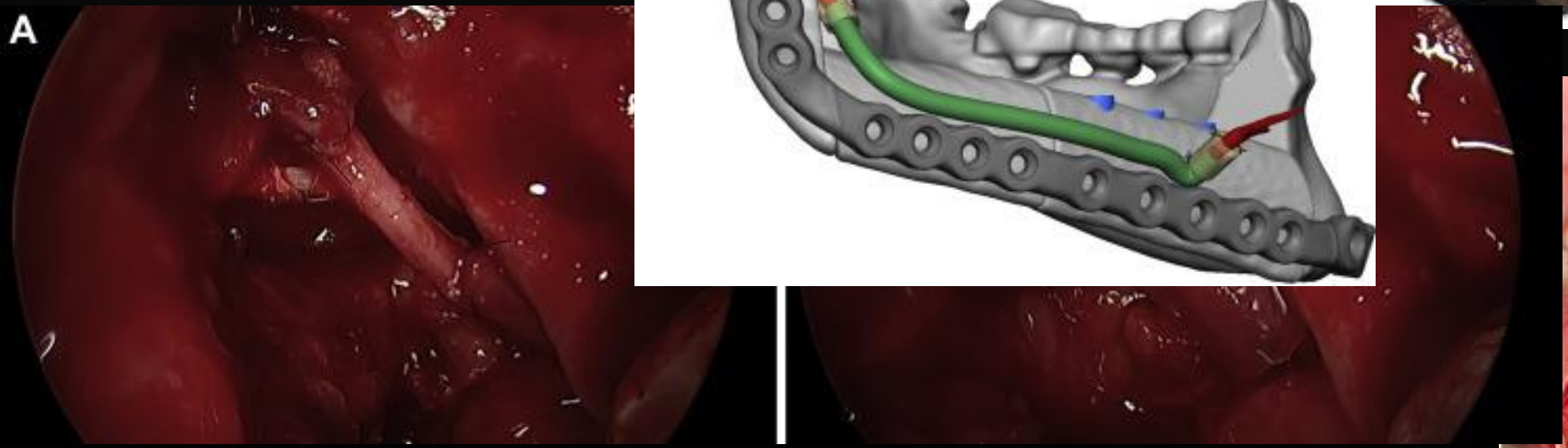
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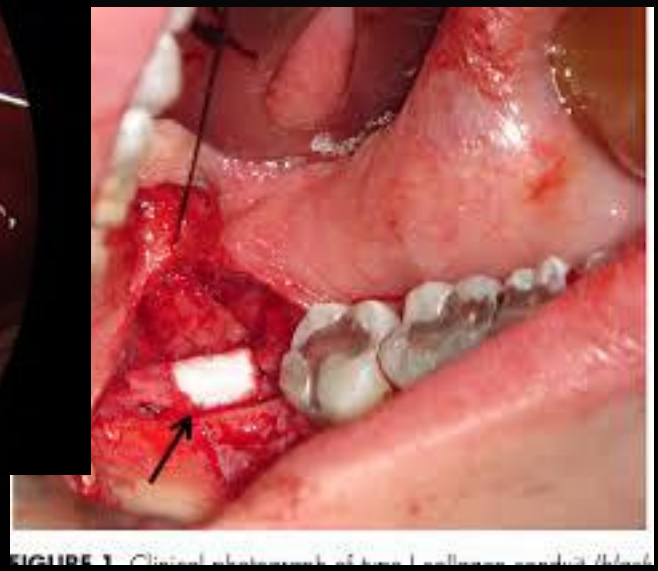

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Mail – tara.renton@kcl.ac.uk | brain connectivity loss chro | Brain imaging reveals how | The pain of sleep loss: A br | The pain of sleep loss: A br

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Research Articles, Behavioral/Cognitive

The pain of sleep loss: A brain characterization in humans

Adam J. Krause, Aric A. Prather, Tor D. Wager, Martin A. Lindquist, and Matthew P. Walker

Journal of Neuroscience 28 January 2019, 2408-18; DOI: https://doi.org/10.1523/JNEUROSCI.2408-18.2018

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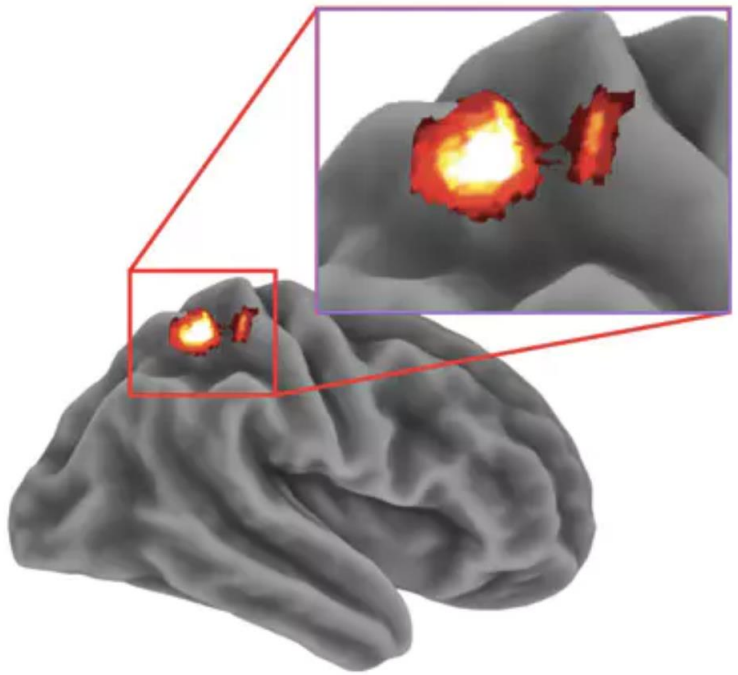
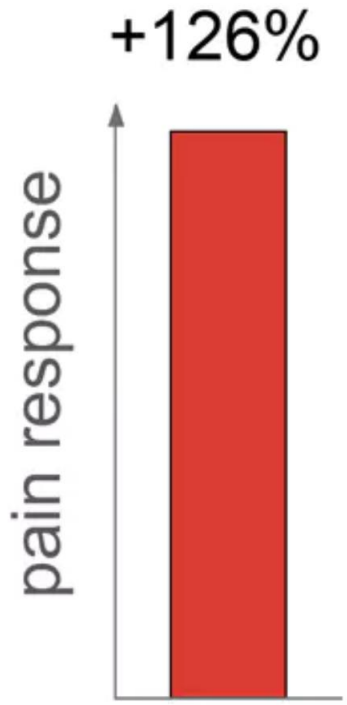




The study also examined the relationship between subtle changes in sleep on a person's pain sensitivity. Using a self-reported survey of over 230

Future Medicine and dentistry?

Tara.renton@kcl.ac.uk

Eric Topol, MD, has written a book about the convergence of the digital revolution and medicine.

It is full of fascinating information and prognostication, but I wish he had given it a better title.

He called it *The Creative Destruction of Medicine: How the Digital Revolution Will Create Better Health Care.*

‘Medicine will not and cannot be “destroyed.” It will be improved and transformed, perhaps, but not destroyed.’

Polygenic risk scoring

- *Polygenic risk scoring is a new tool that will allow doctors to provide precisely tailored medical advice and preventive medicine that matches your specific genetic risk.*

Human Genome Discoveries Reach the Bedside

- In 2000, scientists in with the International Human Genome Project released a rough draft of the human genome to the public. For the first time the world could read the complete set of human genetic information and begin to discover what our roughly 23,000 genes do.
- Mapping the human genome had become a race of time and money in the 1990s, with two competitors at the forefront: the government-funded Human Genome Project, which completed its task in 15 years with more than $3 billion in taxpayer money, and a private company, Celera Genomics, which was financed with $100 million and took less than a decade.
- Both groups announced a rough draft at joint press conference on June 26, 2000.
- In 2003 a "final" draft was released by researchers, and in 2007 more updates to the genome were published by Craig Venter, PhD, chief scientist behind Celera Genomics.

Risk assessment

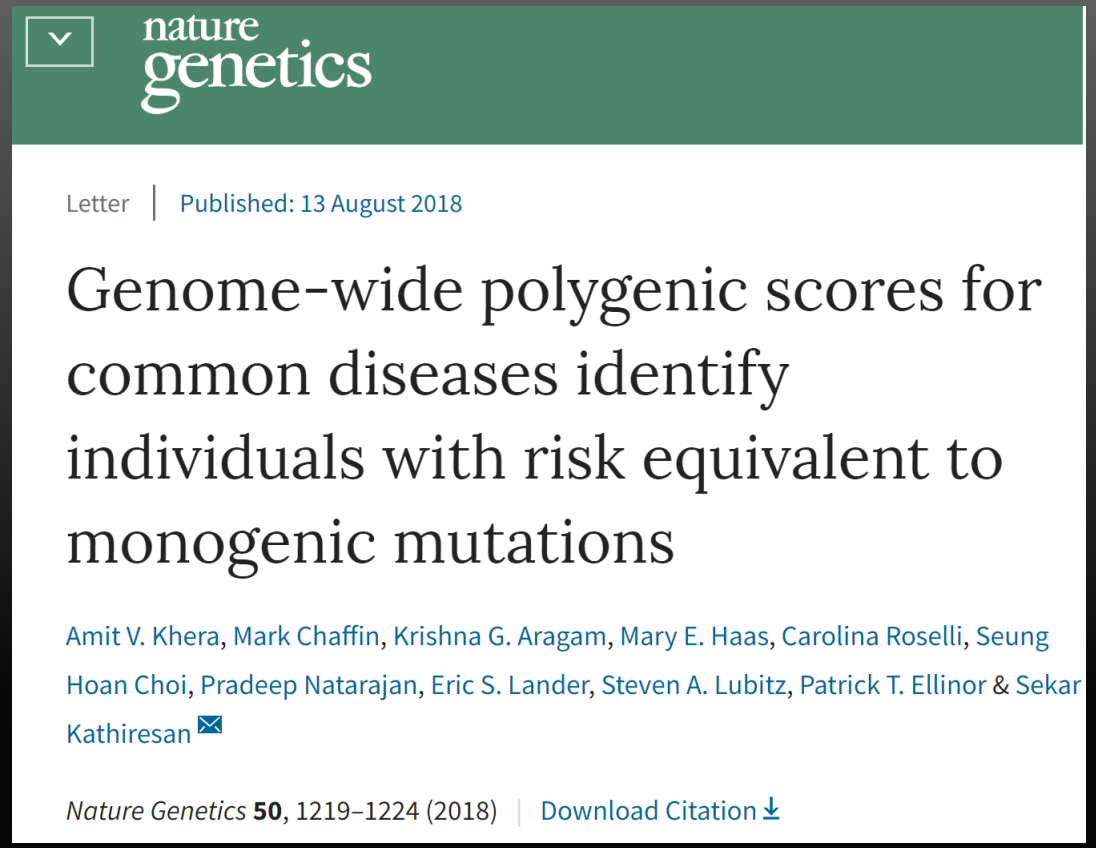
- Traditionally risk assessment for disease was based on current known risk factors and past family medical history
- More recently scientists discovered individual gene mutations that put individual people at dramatically increased risk for specific diseases.
- The most widely known example is probably the BRCA1 gene mutation that increases risk of breast cancer.

Polygenic risk scoring

- This allows the scientists to take *anyone's genome* and calculate your *aggregate risk* for these diseases *even if you don't have one of the known major mutations*. They call it Polygenic Risk Scoring (*poly* = more than one and *genic* = gene). Polygenic Risk Scoring is your total score of all the minor gene variations that increase disease risk

Recent study

- Researchers analyzed 400,000 individual genomes to *"identify genetic variants associated with coronary artery disease, atrial fibrillation, type 2 diabetes, inflammatory bowel disease, or breast cancer."*
- They identified *all the variations that produced even a small bump in disease risk*, not just the major mutations like BRCA1 or the gene for Huntington's Disease.
- Beneath the major mutations are a large number of minor variations that add up to increase in disease risk in individuals with multiple "hits". This pattern of increased risk can cause disease in the absence of an obvious family history.



Amit V. Khera, et al Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nature Genetics*, 2018; DOI: 10.1038/s41588-018-0183-z

- This study only had 400,000 genomes worth of disease association and predictive ability out of the current 7.6 billion humans on earth (= 0.005%). Over time, researchers will expand the number of genomes in the analysis, improve the accuracy and expand the scope of diseases they can predict.

Amit V. Khera, et al Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nature Genetics*, 2018; DOI: 10.1038/s41588-018-0183-z

Artificial Intelligence (AI) on medical science:

- Artificial intelligence is not anew concept. It has been researching and developing for ages now.
- When we get sick we consult with a doctor.
- with associate with AI system, doctor scan have a clear vision to the problems and AI can help the doctors to choose the right medicine for the patient.
- That will reduce the death number of wrong treatment.
- Some people suffer single or multiple complex diseases that they won't have much time but doctors can’t define the problems to start diagnosis.In that case, AI can be very helpful.
- They are able to accurately diagnosis some disease like cancer, tumor, eye problems etc. If you are thinking that AI will cost more than average doctor, then you are probably right. Now, this technology is costly but its development and availability are increasing and +over time will decrease the average medical cost.

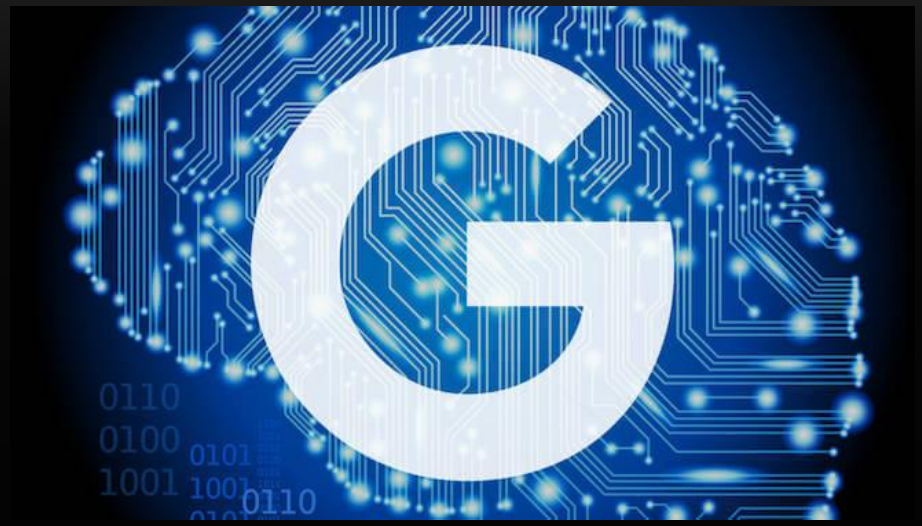
Augmented reality

- The digital contact lens patented by Google aims to change the course of diabetes management by measuring blood glucose levels from tears. While the prototype is going through vigorous testing, regulations must prepare to quickly allow this disruptive technology to enter the market and benefit patients.

- Microsoft Hololens can also change medical education and how we look at the world by projecting digital information onto what we are seeing. A clinic in Germany started experimenting with an application using augmented reality on iPads in the OR. During operations, surgeons can see through anatomical structures such as blood vessels in the liver without opening organs therefore they can perform more precise excisions.

Google Brain

- Ian Pearson wrote in his book, You Tomorrow, about the possibility that one day we will be able to create digital selves based on neurological information.
- It means we could upload our minds to a computer and live on in a digital form.
- As Google hired Ray Kurzweil to create the ultimate artificial intelligence controlled brain, this opportunity should not be so far away. We might have been looking for the secret of immortality in the wrong places.



Recreational Cyborgs

- There are already famous examples of real-life cyborgs, and I am truly convinced that such creatures will not only populate the terrain of sci-fi movies, but they will be everywhere around us in the very near future. The ‘cyborg-craze’ will eventually start with a new generation of hipsters who implant devices and technologies in their bodies just to look cooler.

- Advances in future medical technology will not just repair physical disadvantages such as impaired eyesight but will create superhuman powers from having the eyesight of an eagle to having the hearing of a bat. While a patient wearing implanted defibrillators or pacemakers can also be added to the group of cyborgs, I expect to see more cases when patients ask for the implantation of a certain device without having medical problems.

3D Printing

- There are already examples of 3D printing used in medicine. Through the e-NABLING the Future project, a global network of passionate volunteers enable volunteers, doctors or anyone on the field to make a difference by literally “giving a helping hand” to those in need by sharing 3D Printing designs, video tutorials and other information about building prosthetic hands. Success stories come from all over the world: there are now children and adults with super-hero style or more traditionally shaped prosthetic hands in Chile,

Gamifying behaviour change

- Adherence and compliance represent crucial issues in improving patients' health and decreasing the cost of delivering healthcare. Several start-ups have targeted this issue with different solutions such as a pill bottle that glows blue when a medication dose should be taken and red when a dose is missed (winner of the Healthcare Innovation World Cup); or tiny digestible sensors that can be placed in pills and can transmit pill digestion data to physicians and family members.
- While patients do not like the term adherence as they want to be partners with their caregivers rather than following orders, health insurance companies will use more and more data to check whether the patients comply with their prescriptions to decrease their insurance costs. The wildly popular Pokemon Go motivates people to walk more which might lead to fighting obesity while playing a game.

New diseases

- Regarding technological development, there is always a risk for the emergence of so far unknown illnesses and conditions. New types of diseases will appear due to the excessive use of virtual reality solutions in gaming and other industries including healthcare.
- Examples include virtual post-traumatic stress disorder (v-PTSD) which might be the diagnosis for gamers who participate in large virtual battles wearing VR masks (such as Call of Duty of Battlefield) and experience similar symptoms as those soldiers who fought in real wars. Virtual reality as an extension of online activity and particularly that of gaming might also cause addiction. Expect to see ICD codes assigned to such new conditions.

New diseases

- Eosinophyllic vaping lung disease
- Ebola

Real-time diagnostics

- The intelligent surgical knife (iKnife) was developed by Zoltan Takats of Imperial College London and works by using an old technology where an electrical current heats tissue to make incisions with minimal blood loss. With the iKnife, the vaporized smoke is analyzed by a mass spectrometer to detect the chemicals in the biological sample. This means it can identify whether the tissue is malignant real-time.
- Surgeons will love this surgical Jedi knife which can significantly reduce the length of operations.

Holographic data input

- While better and better data input solutions arise, we will probably not even need hardware to add data to a laptop or PC as screens and keyboards will be projected on the wall or on the table making it simple and accessible everywhere in the clinical settings.
- Holographic and virtual keyboards will make us forget about smartphones and tablets. Only small projectors will be needed, while the data will be stored exclusively in the cloud.

Crowdsourcing through social media

- Medical communication is something that affects all patients and medical professionals worldwide without exceptions. This is one reason why social media has the potential to become a huge “mind machine” making it possible to transmit, share, crowdsource and store medical pieces of information either for e-patients or medical professionals if such social platforms are used in a proper way. Don’t underestimate the power of digital/medical communication.

Multi-functional radiology

- Radiology is one of the fastest growing and developing areas of medicine, therefore this might be the specialty in which we can expect to see the biggest steps in developments.
- One multi-functional machine will be able to detect plenty of medical problems, biomarkers and symptoms at once.
- Naturally, artists and movies are already way ahead of us: check out the machine used in the film, Elysium. With one quick check-up it tells you what percentage of your cells are cancer free.

Machine learning

- Replacement of radiologists and pathologists?

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Monitoring

- **Monitoring.** Sensors now available or in development can do amazing things. They can monitor chronic diseases and provide remote electronic early warning of medical crises. Biosensors in cars could prevent accidents by detecting impending seizures, heart attacks, diabetic reactions, etc. Monitoring is a good thing, but you can have too much of a good thing, and some of what Topol advocates smacks of overkill. One of his patients sends him e-mails with 3 or 4 daily measurements of everything from blood pressure to oxygen saturation. Topol monitors his own sleep witha Zeo device. This is “nice to know” information but its impact on health outcomes is not so clear.
- **Lab on a Chip.** A biosensor can be incorporated into a cell phone’s SIM card to do everything from detecting malaria to analyzing electrolytes. A phone camera can take a picture of a skin lesion and use a sophisticated algorithm to determine if it is melanoma. Digitizing breath might detect lung cancer. A high-tech “tattoo” worn on the skin can be read by your cell phone to measure your blood sugar.

- **The Office Visit of the Future.** Virtual office visits may replace face-to-face encounters. Tools like video chats, telemedicine, and e-mail are already available.

- **Electronic Health Records as a Research Platform.** Electronic databases have enormous potential: they can be useful in drug development, post-marketing surveillance, gathering statistics about disease, and monitoring adequacy of treatment. Just one example: if every patient on a drug were entered into a single database along with comparable patients not on the drug, even a rare adverse effect could be detected, and less rare effects could be spotted earlier. If we could include DNA sequencing in that database, we might learn which genotypes were susceptible to a certain side effect and could avoid prescribing the drug to such patients. We have the capability to do this today, although implementing it would be far from easy.

Privacy issue/ data security

Hacking into databases is a danger to patient privacy today, and the danger will grow in proportion to the amount and value of the data. No one has yet built a truly hack-proof system, and it’s unclear that if it will ever be truly possible. As with medicine itself, the benefits must outweigh the risks. But consider what it would be worth to the large insurance companies and employers of the future, if they could discriminate based on genetic profiles and other private medical information.

- **Treating the Individual.** CAM providers claim to tailor their treatments to the individual, but they are mainly making things up or relying on pseudoscience. In the medicine of the future, we will have truly individualized treatment based on scientific reality.

- **Doctor Bashing** Topol criticizes current medical practice for relying too heavily on randomized trials and using population-based rather than individualized treatments. He speaks of “Resistance from the priesthood of medicine.” He says “Of all the professions represented on the planet, perhaps none is more resistant to change than physicians.”
- I think that’s demonstrably false. Medical practice is constantly changing and evolving in response to new information and new technologies. It is true that it takes an average of 17 years from medical discovery to daily clinical practice and that this can be accelerated. We can do better. But so far there are very few instances where we have the knowledge to tailor prescriptions to a patient’s genome, and treatments based on studies of large groups are surely better than guesswork.

- **Genomics.** Our ability to sequence patients' genomes opens up whole new worlds. Topol characterizes genome analysis as "hypothesis-free" research, but I don't think that's quite accurate. We can screen lots of data looking for the unexpected, but we are still working with hypotheses about how that screening can produce results. Topol is enthusiastic about currently available direct-to-consumer genetic testing; I'm not so sanguine. He says if his genome showed a high risk of blood clots he would be more inclined to get up and walk around on long flights. Maybe. Does genomic testing really change behavior? At least one study showed it didn't, but Topol was impressed that these patients expressed an increase in the *intent* to undergo screening tests like colonoscopy. I think supervision and interpretation of these tests by doctors is a reasonable precaution; Topol thinks it would constitute unfair interference with health freedom.
- Genetic analyses can assist in drug development by teasing out who benefits and who gets rare side effects. With knowledge of gene specific effects, some rejected drugs might have been approved for a subset of patients.
- Topol recognizes that it will not be a simple matter of finding a gene for every disease. Genetics is far more complicated: many conditions are multifactorial, genes interact with each other, and environmental factors affect gene expression. David Gorski's recent article explains the complexity of genetic factors in cancer. In one study he cites, multiple biopsy samples revealed different genetic profiles in different parts of the primary tumor and metastases. Personalized treatment based on genetic analysis of a single biopsy would fail.

- **The Nicholas Volker Case.** Topol describes this as the first instance of the life-saving power of genomic medicine. A child with a unique bowel disorder was found to have a mutation and was treated with an umbilical cord blood stem cell transfusion. His recovery was attributed to DNA sequencing, but doctors had already been contemplating this stem cell treatment before the mutation was detected. The outcome might have been the same without DNA testing.

Nature paper on polygenetics

- A key public health need is to identify individuals at high risk for a given disease to enable enhanced screening or preventive therapies. Because most common diseases have a genetic component, one important approach is to stratify individuals based on inherited DNA variation[1]. Proposed clinical applications have largely focused on finding carriers of rare monogenic mutations at several-fold increased risk. Although most disease risk is polygenic in nature[2,3,4,5], it has not yet been possible to use polygenic predictors to identify individuals at risk comparable to monogenic mutations.
- Here, we develop and validate genome-wide polygenic scores for five common diseases. The approach identifies 8.0, 6.1, 3.5, 3.2, and 1.5% of the population at greater than threefold increased risk for coronary artery disease, atrial fibrillation, type 2 diabetes, inflammatory bowel disease, and breast cancer, respectively. For coronary artery disease, this prevalence is 20-fold higher than the carrier frequency of rare monogenic mutations conferring comparable risk[6]. We propose that it is time to contemplate the inclusion of polygenic risk prediction in clinical care, and discuss relevant issues.

- **Cautious Optimism**
- The future of medicine holds great promise. I don’t mean to be a wet blanket, but the challenge will be to temper our enthusiasm with good judgment. We can’t assume unalloyed benefit from every technological advance. Just because we *can* do something like constantly telemonitoring everything from our serum potassium level to our blood pressure doesn’t mean we *should* do it, or that it would be a good use of limited health care funds. We don’t want to create a world of cyberchondriacs. Data overload is a problem. Privacy is a major concern. Forgoing face-to-face human interaction may have significant downsides. What’s called for is what scientific medicine has always called for: cautious enthusiasm with scientific testing. Not “the destruction of medicine,” but the natural continuation of it.

(CAR) T-cell Immunotherapies

- There have been such tremendous advancements in treatments for blood cancers like leukemia and lymphoma, that the five-year survival rate for children with Acute lymphocytic leukemia (ALL) is now over 85 percent. And starting in 2017, those kinds of numbers may leap even higher.
- For the first time, pending FDA approval, chimeric antigen receptor (CAR) T-cell therapy will be made available to "high-end" cancer centers around the country. In this kind of cellular immunotherapy, white blood cells called T-cells are extracted from a patient, treated at a special laboratory, and then returned to the patient to fight cancer cells. Trials on kids with ALL have proven very successful, with high rates of complete remission. The Leukemia & Lymphoma Society notes that studies of CAR T-cell therapy on multiple myeloma,chronic lymphocytic leukemia (CLL), and some types of non-Hodgkin lymphoma (NHL) have also been "very promising," as well.

Synthetic Blood

From prosthetic limbs to artificial hearts, pacemakers to ear implants, we've figured out how to replace darn near every part of the human body. But until fairly recently, blood was a bit of a pipe dream. Not so anymore.In 2017, England's National Health Service (NHS) will conduct early safety trials, in which about 20 people are given small amounts of synthetic blood made from stem cells. The short-term goal is to create red blood cells to treat specific conditions and illnesses, like sickle cell anemia. The long-term goal? NHS scientists hope to make enough for transfusions for people with rarer blood types.

Mobile Stroke Treatment Units

- When a stroke hits, every second counts; it's estimated you lose about two million neurons each minute after the event, and the longer you go untreated, the worse the damage to your brain. That's why a Mobile Stroke Treatment Unit (MSTU or MSU) could be a lifesaver.
- Usually staffed by paramedics, a nurse, and a medical imaging specialist, among other emergency personnel, an MSTU is essentially an ambulance dedicated to the fast diagnosis and treatment of strokes. When a dispatcher calls in a stroke, the MSTU is mobilized to the patient's home. Once it arrives, the team is able to determine whether a stroke is caused by a blood clot, administer a drug to dissolve that clot, and then bring the patient to an appropriate hospital.
-
- Early studies of response time are promising, and there are currently units in Cleveland, New York, Houston, and Denver, with more coming every day. In fact, one source reports that by late 2017, an MSTU will be available to more than 40 percent of major-city emergency rooms

Interoperability

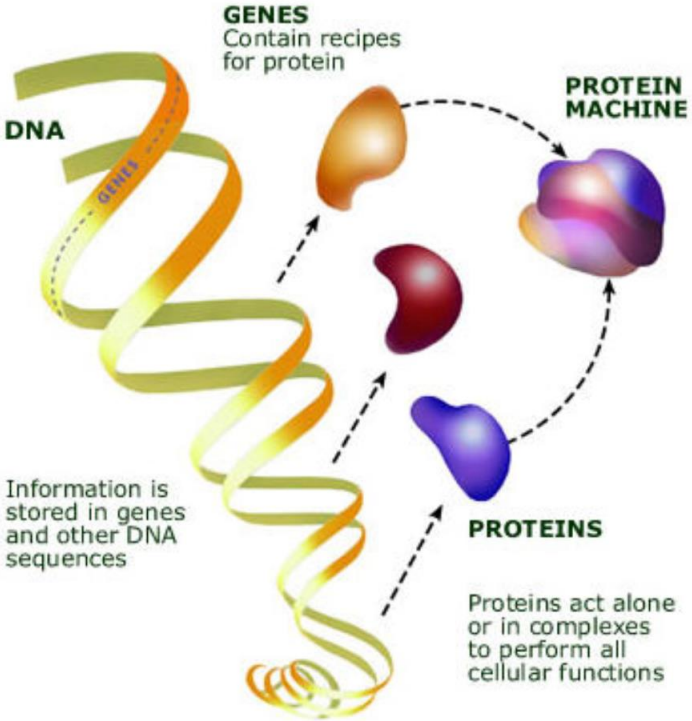
- If there's one advancement medical experts and the press seem most excited about, it's interoperability, or, the ability of health care information technologies—like a hospital's digital systems—to communicate with each other. For those who have wondered why the billing department can't get on the same page as your doctor, this is the breakthrough for you.

- Set to debut in 2017, Fast Healthcare Interoperability Resources (FHIR) is a kind of tool dedicated to saving money and lives by improving the speed and efficiency of health data transferal. Essentially, instead of transferring entire documents, which causes a backup, FHIR transfers specific bits of health care information—a word, a code—from one place (ex: your doctor) to another (ex: billing). This means health care workers don't have to go through tons of extraneous information to get the data they want, making your experience faster and your records, more accurate.
- On a more personal level, the technology will make it easier to create health apps, as well, which could filter down to patients in years to come.

OMICs for idiots - genomics

- DNA in the genome is only one aspect of the complex mechanism that keeps an organism running – so decoding the DNA is one step towards understanding the process. However, by itself, it does not specify everything that happens within the organism.
- The basic flow of genetic information in a cell is as follows. The DNA is transcribed or copied into a form known as “RNA”. The complete set of RNA (also known as its transcriptome) is subject to some editing (cutting and pasting) to become messenger-RNA, which carries information to the ribosome, the protein factory of the cell, which then translates the message into protein.

Figure 1. Genes, proteins, and molecular machines



Proteomics

- Proteins are responsible for an endless number of tasks within the cell. The complete set of proteins in a cell can be referred to as its proteome and the study of protein structure and function and what every protein in the cell is doing is known as proteomics. The proteome is highly dynamic and it changes from time to time in response to different environmental stimuli. The goal of proteomics is to understand how the structure and function of proteins allow them to do what they do, what they interact with, and how they contribute to life processes.
- An application of proteomics is known as protein “expression profiling” where proteins are identified at a certain time in an organism as a result of the expression to a stimulus. Proteomics can also be used to develop a protein-network map where interaction among proteins can be determined for a particular living system.

Metabolomics

- Metabolomics is one of the newest ‘omics’ sciences. The metabolome refers to the complete set of low molecular weight compounds in a sample. These compounds are the substrates and by-products of enzymatic reactions and have a direct effect on the phenotype of the cell. Thus, metabolomics aims at determining a sample’s profile of these compounds at a specified time under specific environmental conditions.
- Genomics and proteomics have provided extensive information regarding the genotype but convey limited information about phenotype. Low molecular weight compounds are the closest link to phenotype.
- Metabolomics can be used to determine differences between the levels of thousands of molecules between a healthy and diseased plant. The technology can also be used to determine the nutritional difference between traditional and genetically modified crops, and in identifying plant defense metabolites.
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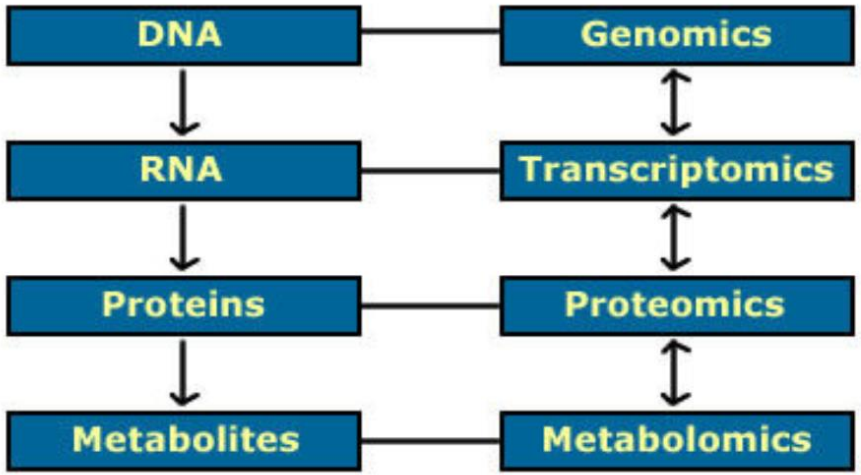
Example of metabolic network

Figure 2. Example of a metabolic network model for *E. coli*



- Genomics provides an overview of the complete set of genetic instructions provided by the DNA
- Transcriptomics looks into gene expression patterns.
- Proteomics studies dynamic protein products and their interactions
- Metabolomics is also an intermediate step in understanding organism’s entire metabolism.