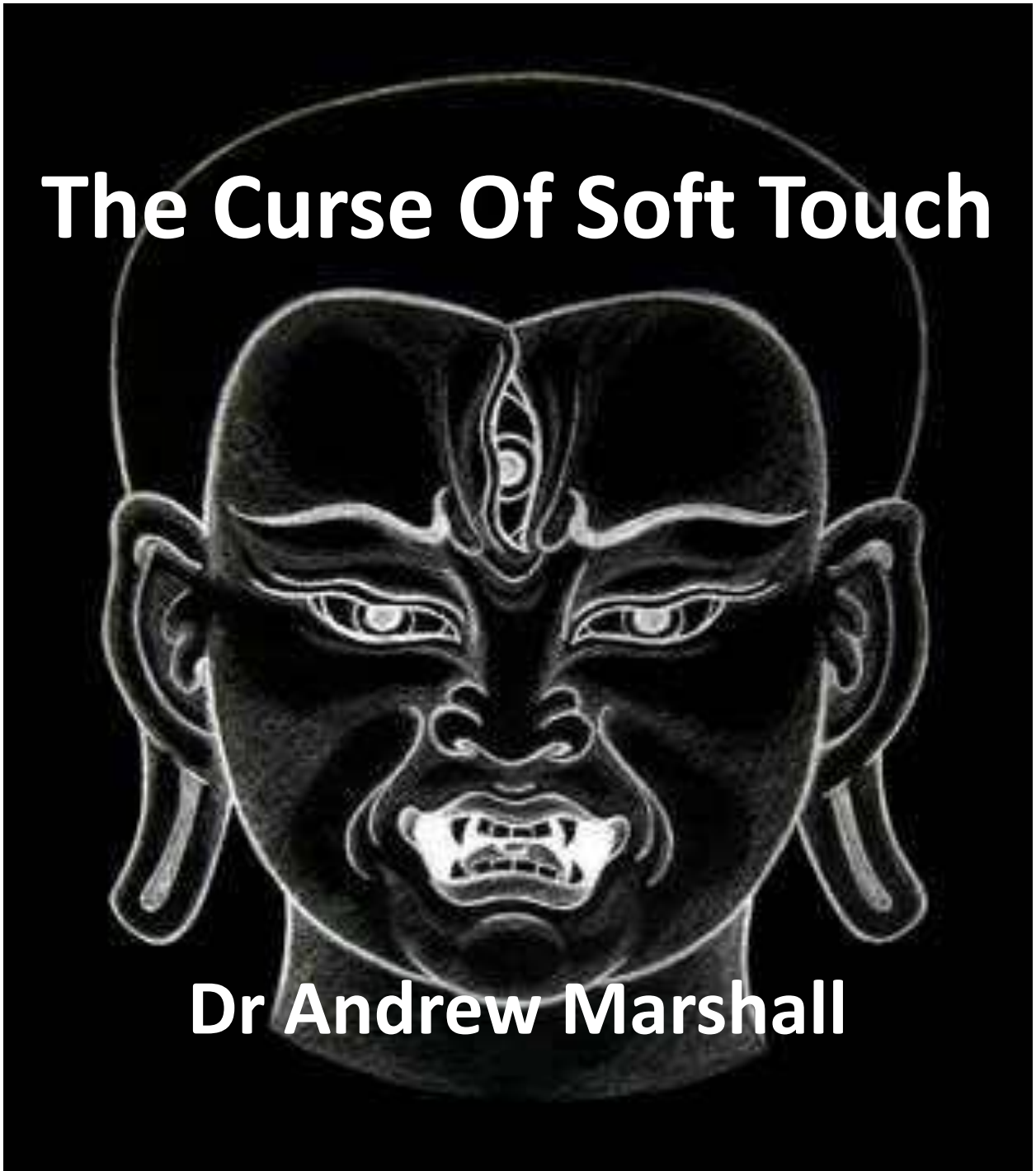
The Curse Of Soft Touch



Dr Andrew Marshall

- Consultant Clinical Neurophysiologist
  - SRFT / MFT
- Academic
  - UoM (Painful Diabetic Neuropathy and Neuropathy Diagnosis)
  - LJMU (Francis McGlone, Microneurography & Psychophysics)
  - WCFT/UoL (Manohar Sharma, Andreas Goebel)

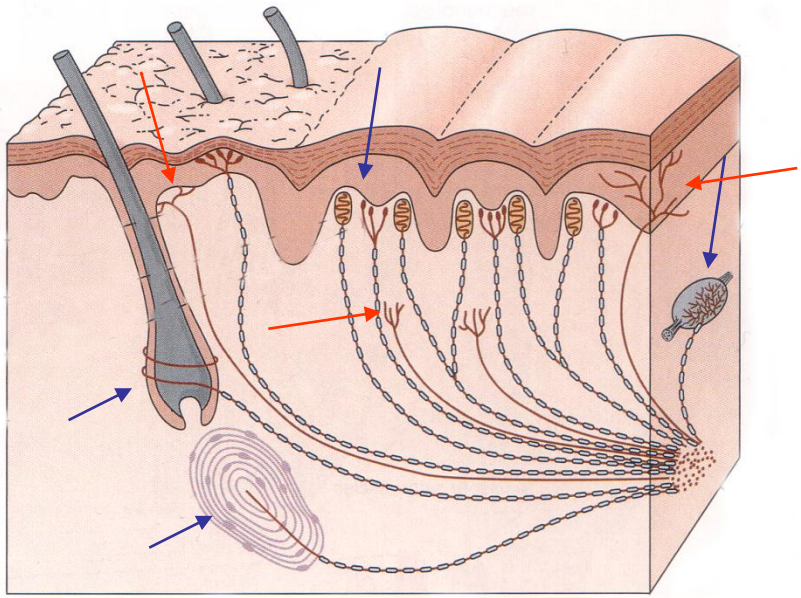
- *Francis McGlone Microneurography – 7T grant*

- *'Developing a model to evaluate C-Tactile fibre contribution to allodynia and for testing new topical Medications – a microneurography and psychophysical study.'* 2015

- *'Investigating the second order spinal projection pathway of C-Tactile afferents and their contribution to pain processing.'* 2017

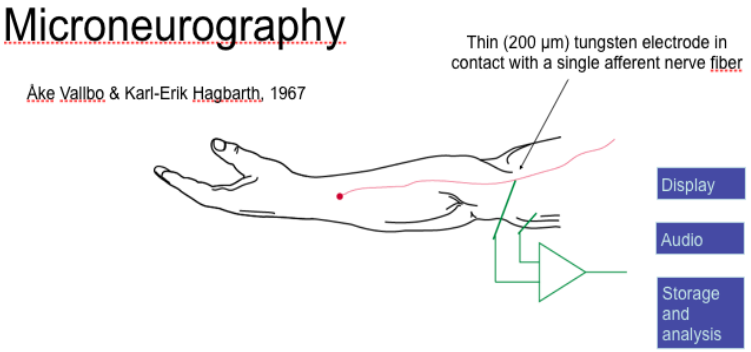
Soft Touch

Sensory receptor units in the human skin



Thick fast myelinated (Ab)
~35-60 m/s
Mechanoreceptors
- touch (SAI, SAII, RA)
- vibration (Pacinian, Pc)
- hair movements (Hair afferents)
Thin myelinated (Ad) ~ 5-35 m/s
Temperature: cold
Pain, Touch?

"A-fibers"



Slow unmyelinated (C) ~0.4 – 2.0 m/s
Temperature: warm, cold
Pain
Low threshold mechanical (CT) in hairy skin
- cats, rodents, primates
- man (1990s)

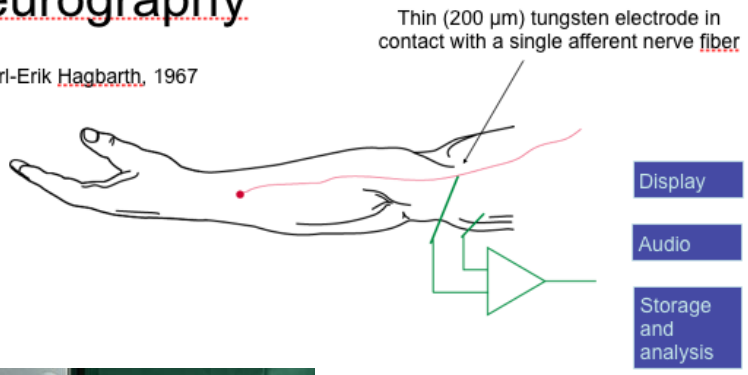
"C-fibers"

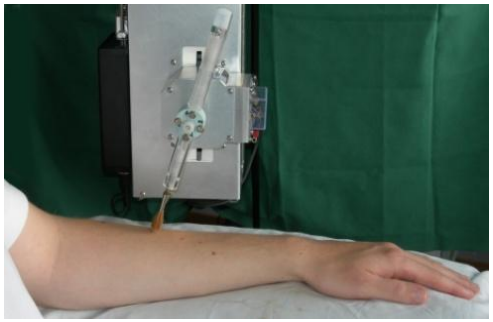
Fast and slow touch

How to Study C-Tactile Fibres

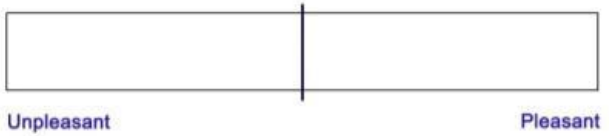
Microneurography

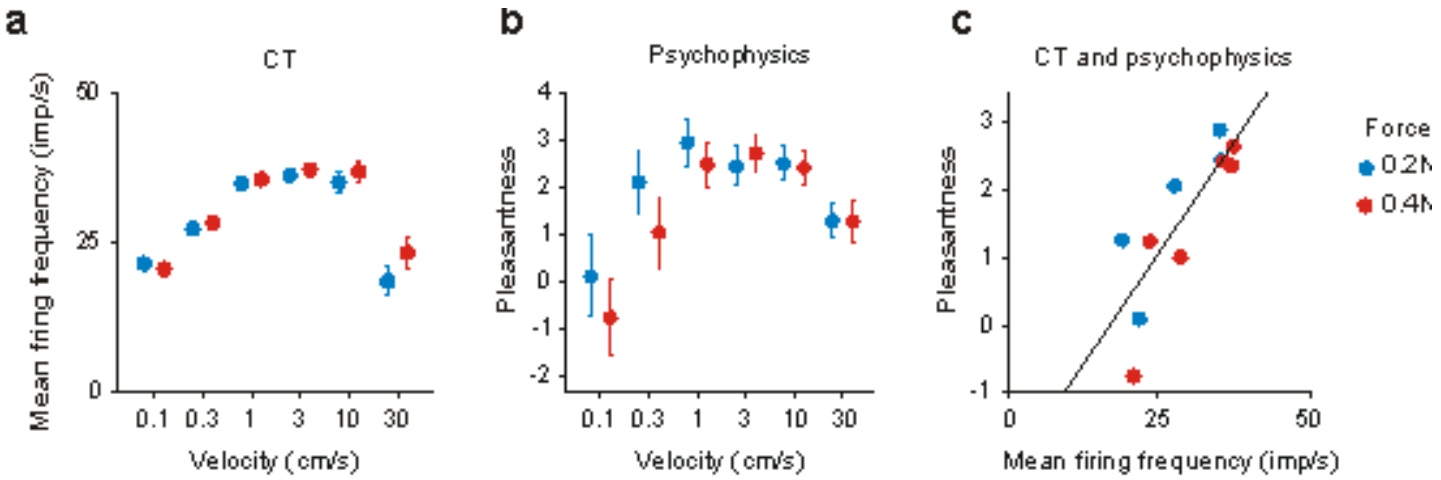
Åke Vallbo & Karl-Erik Hagbarth, 1967





Psychophysics

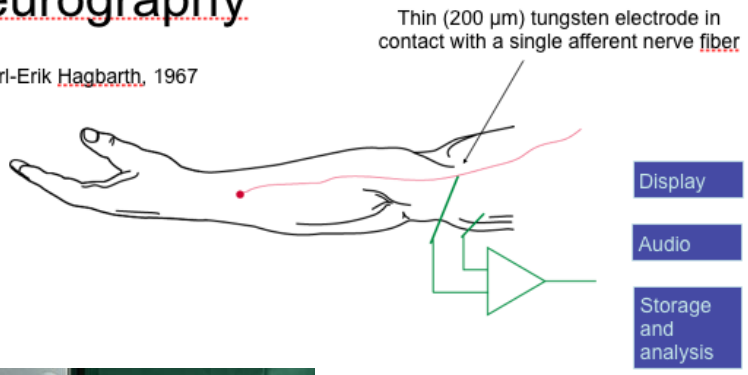


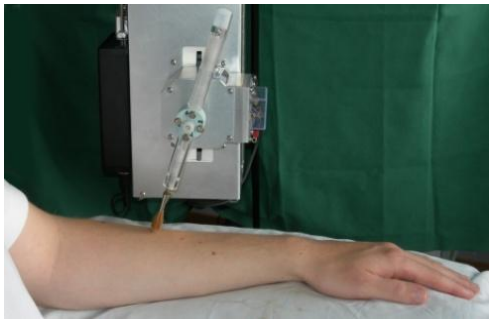


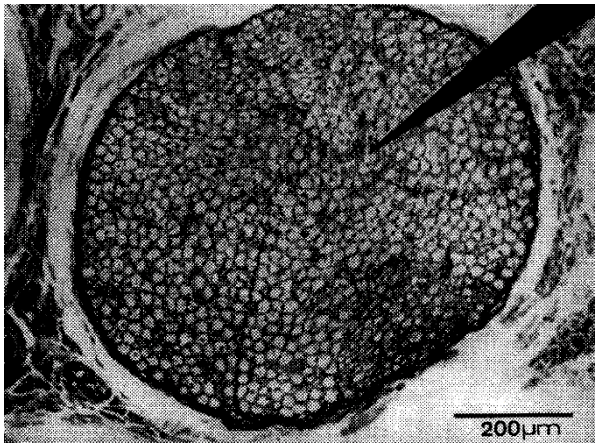
Löken et al., Nature Neuroscience 2009

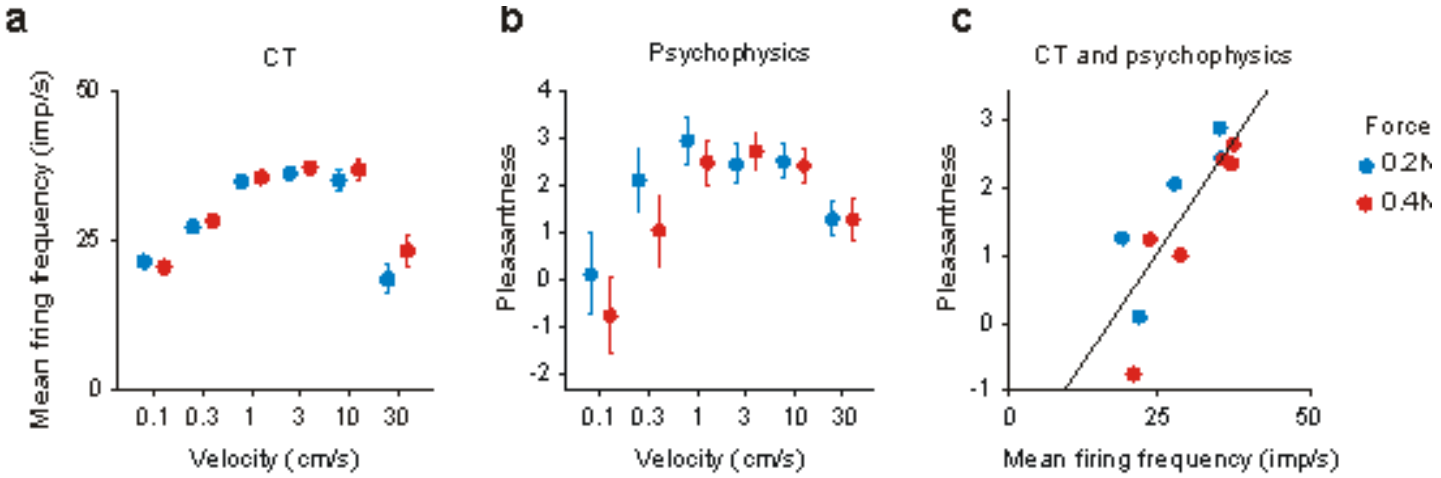
Microneurography

Åke Vallbo & Karl-Erik Hagbarth, 1967









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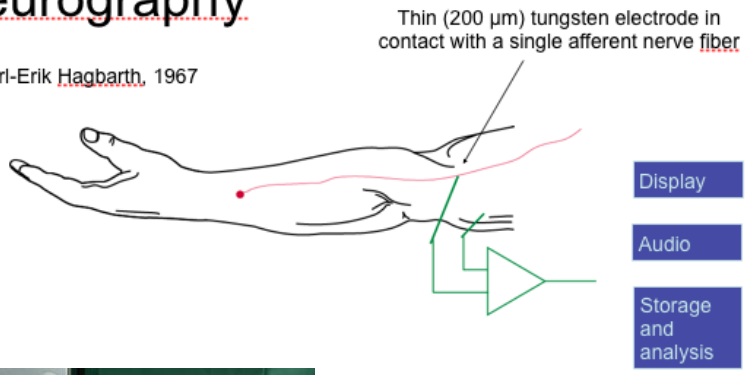
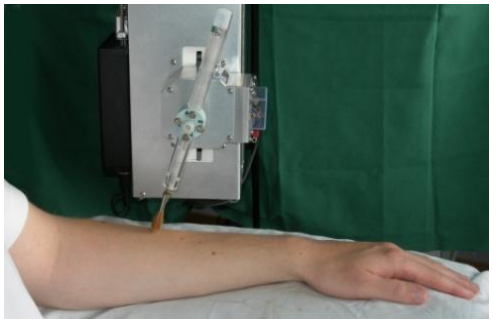
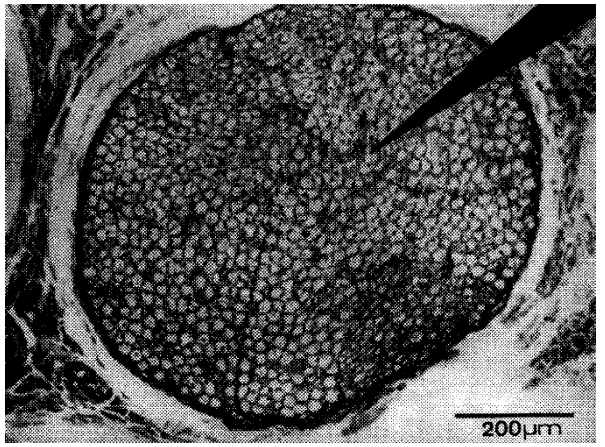
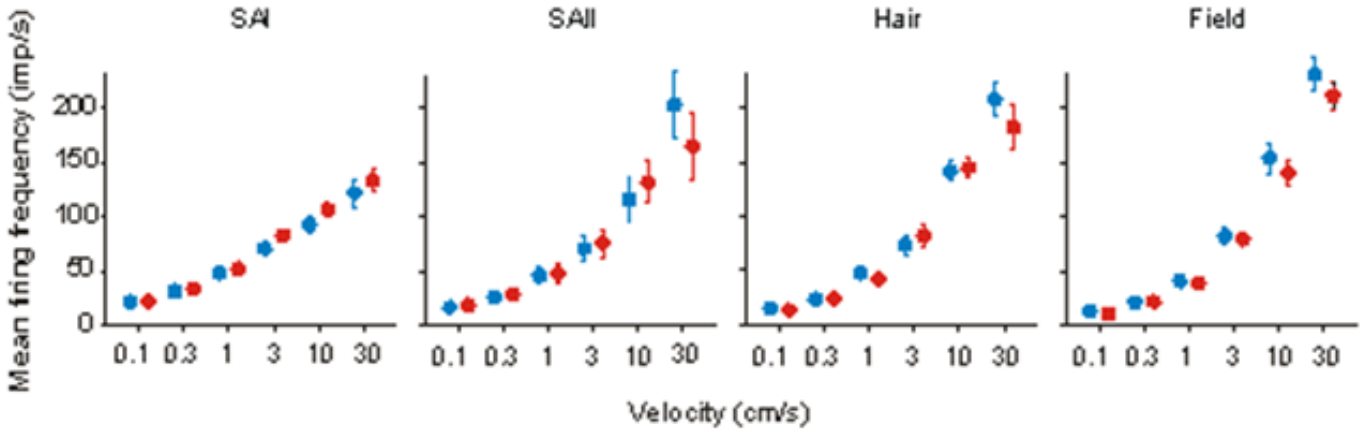




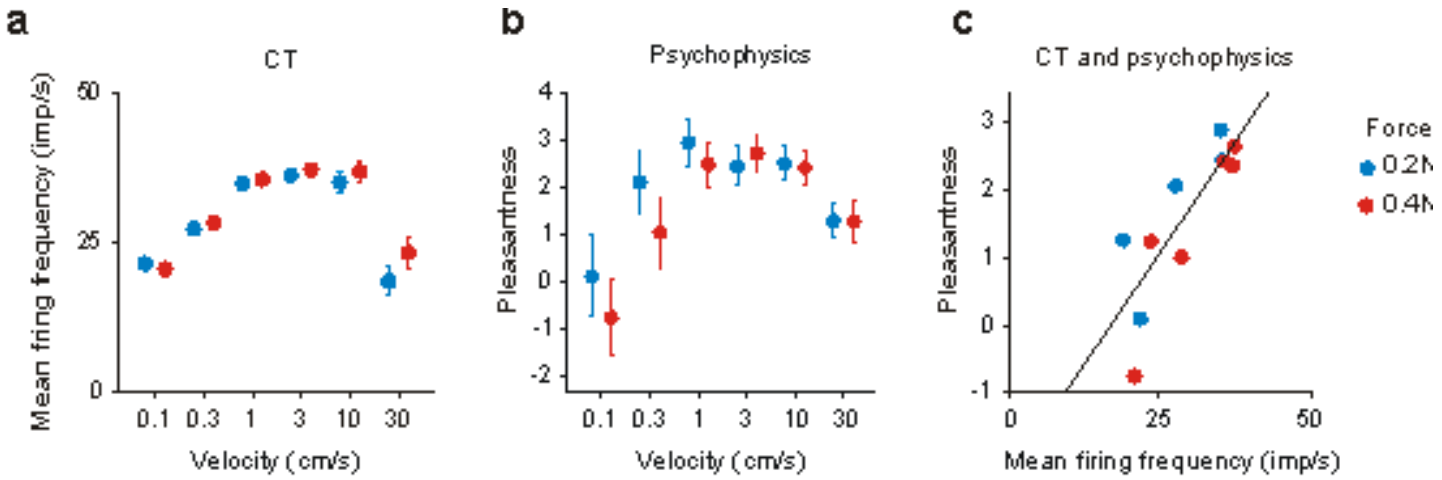




Löken et al., Nature Neuroscience 2009

The ”affective touch hypothesis”

CT afferents have a role to signal affective (pleasant, social, affective) aspects of light touch



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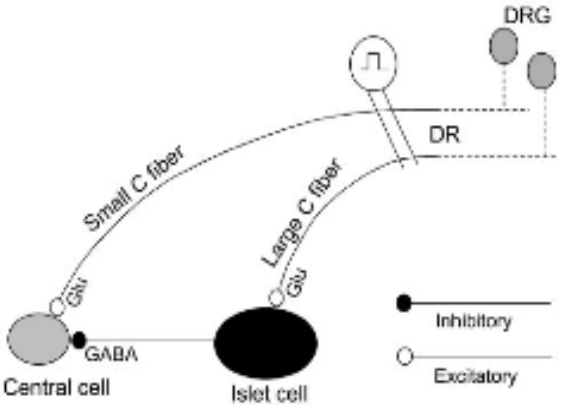
Pain modulatory role of C-LTMRs

A Specific Inhibitory Pathway between Substantia Gelatinosa Neurons Receiving Direct C-Fiber Input

8752 • The Journal of Neuroscience, September 24, 2003 • 23(25):8752–8758

Yan Lu and Edward R. Perl



Genetic identification of C fibres that detect massage-like stroking of hairy skin *in vivo*

Pharmacogenetic activation of Mrgprb4-expressing neurons in freely behaving mice promoted positively reinforcing and/or anxiolytic behaviour

doi:10.1038/nature11810

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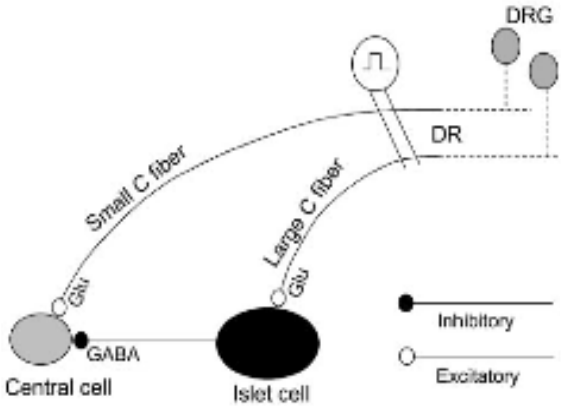

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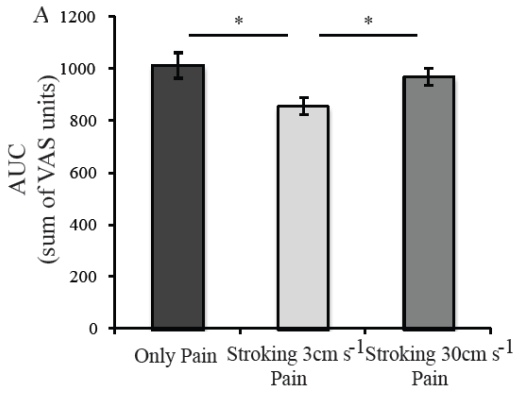


Slow brush stimulation reduces adult pain
Liljencrantz et al 2017

Slow brush stimulation reduces neonatal pain ERP and heart rate
McGlone, Walker & Slater

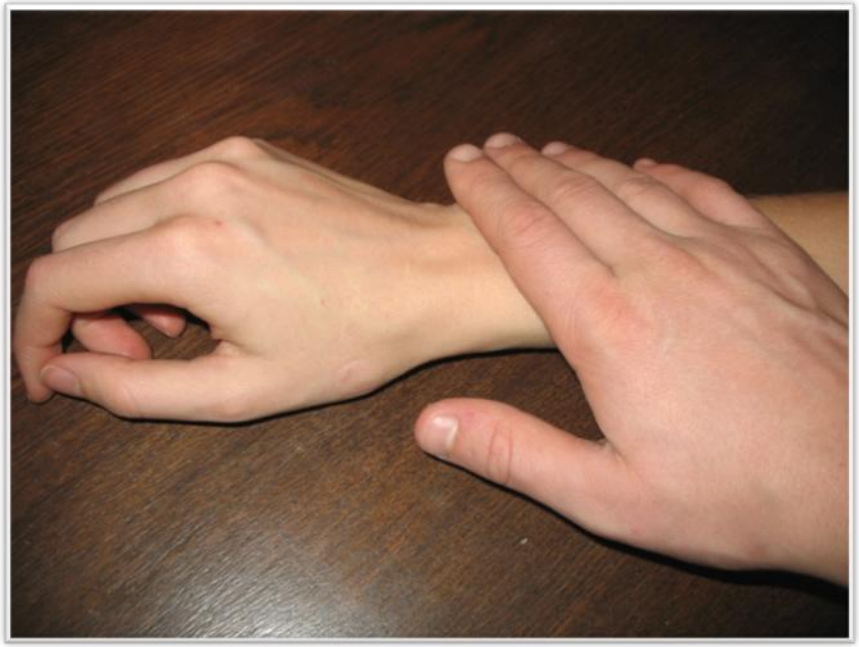
C-tactile fibres and Pain

- Group of C-fibres, *C-tactile afferents*, that 'signal' positive hedonic aspects of touch
  - Anatomy and Physiology of C-tactile afferent pathways
- Evidence that these may modulate nociceptive pathways
- Selective activated these fibres may be useful in the treatment of some pain
- However…

The Curse

When Soft Touch Hurts
The Paradox that is Allodynia

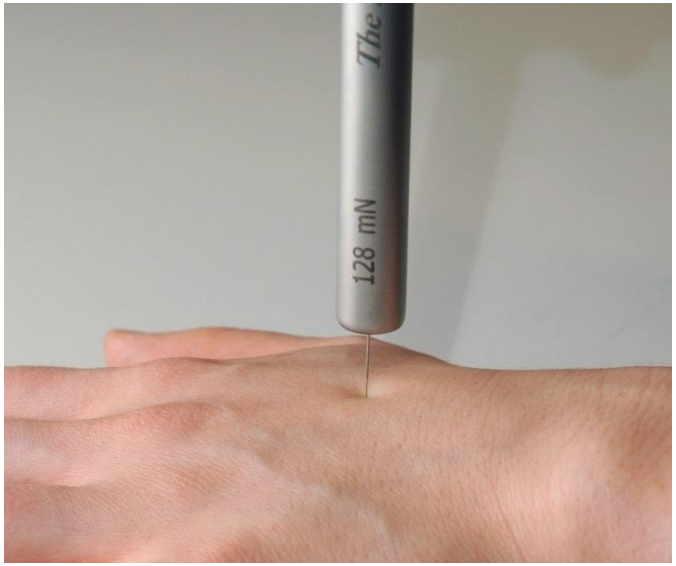
- IASP definition
- "Pain due to a stimulus that does not normally provoke pain"

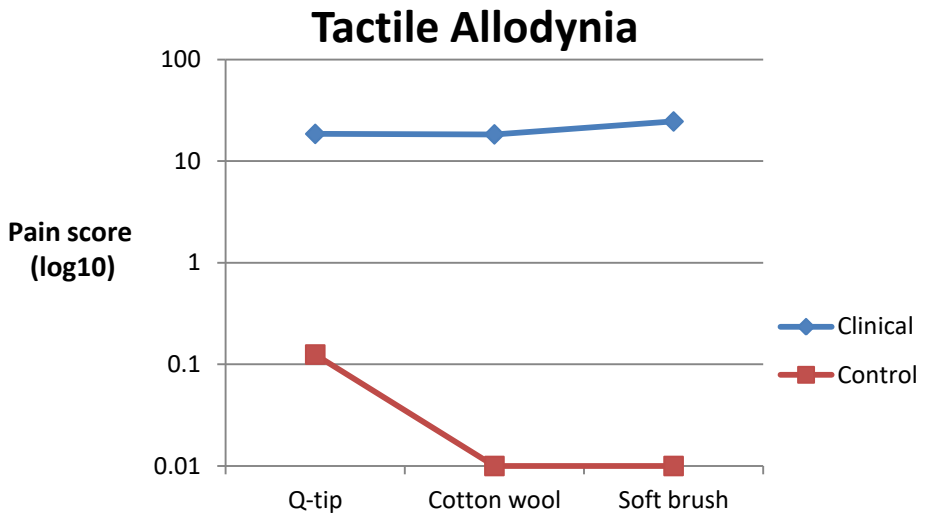


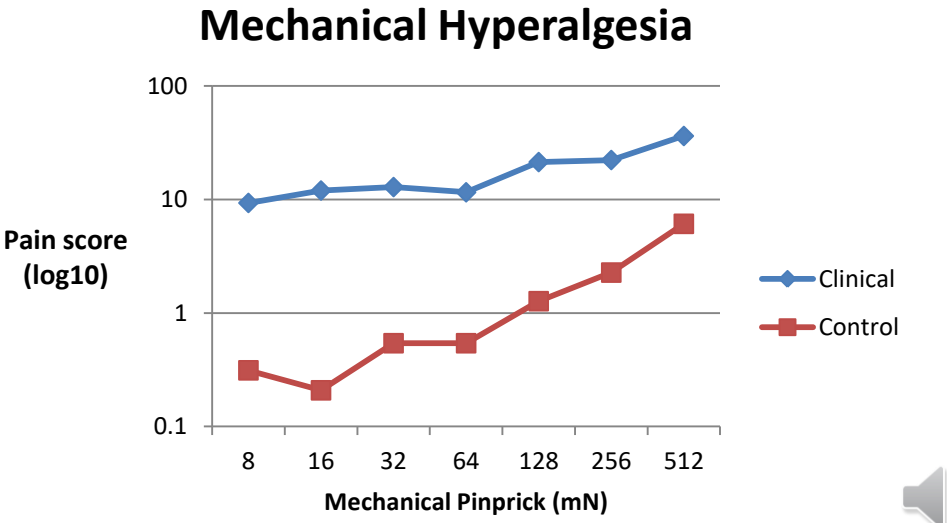
Typically a burning, tender sensation during soft stroking of the affected skin

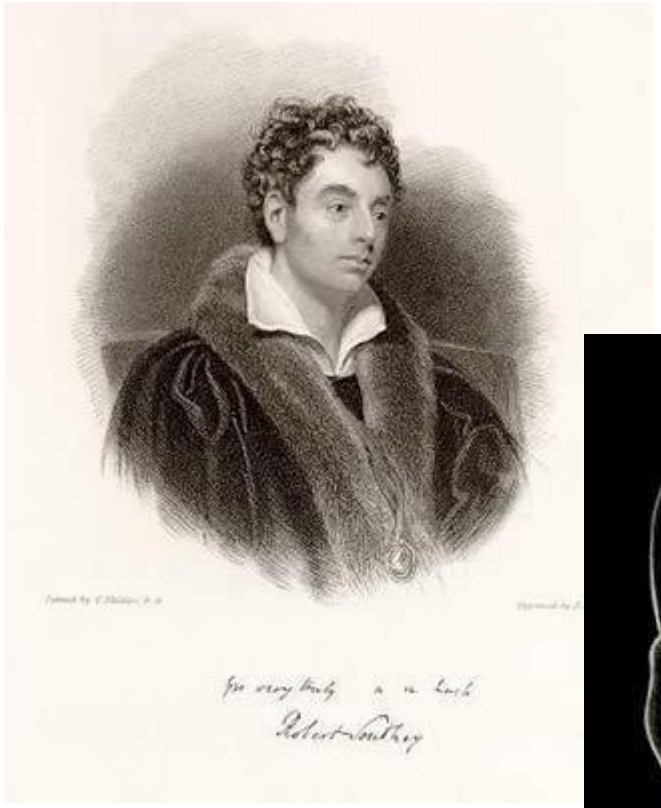
Mechanical Testing

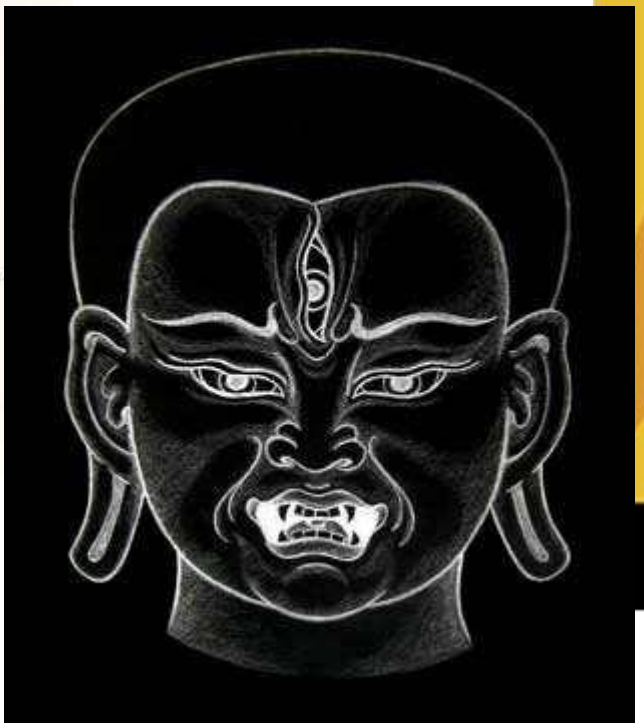
MPS: Mechanical Pain Sensitivity

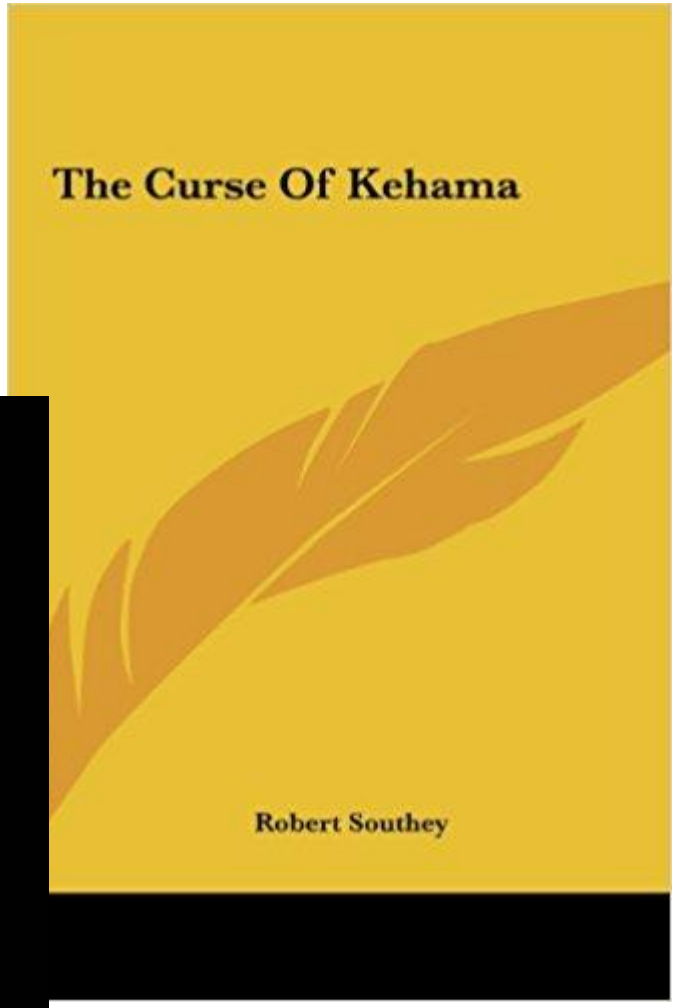












’makes its victim ward off his daughters embrace *'as though it were an enemy's blow’*

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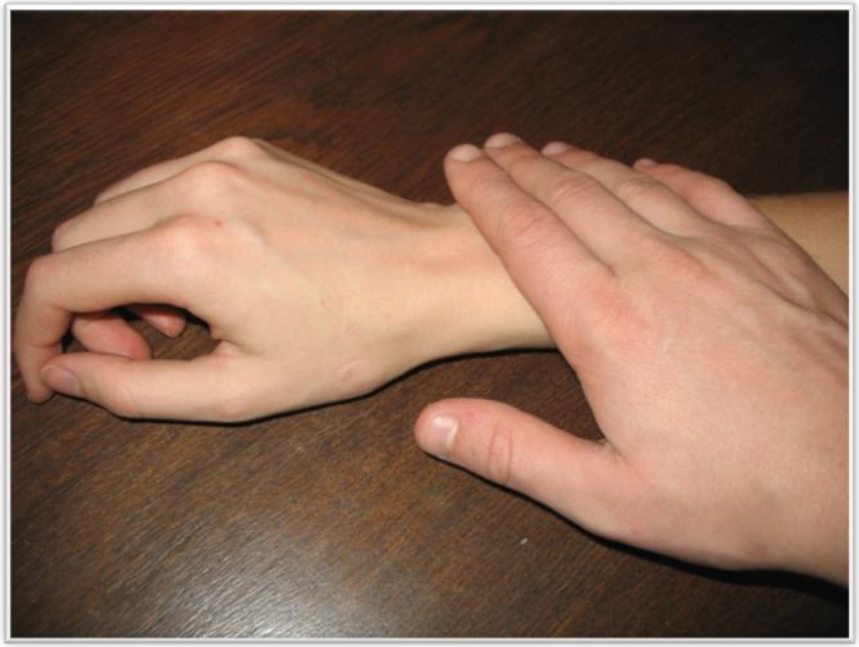
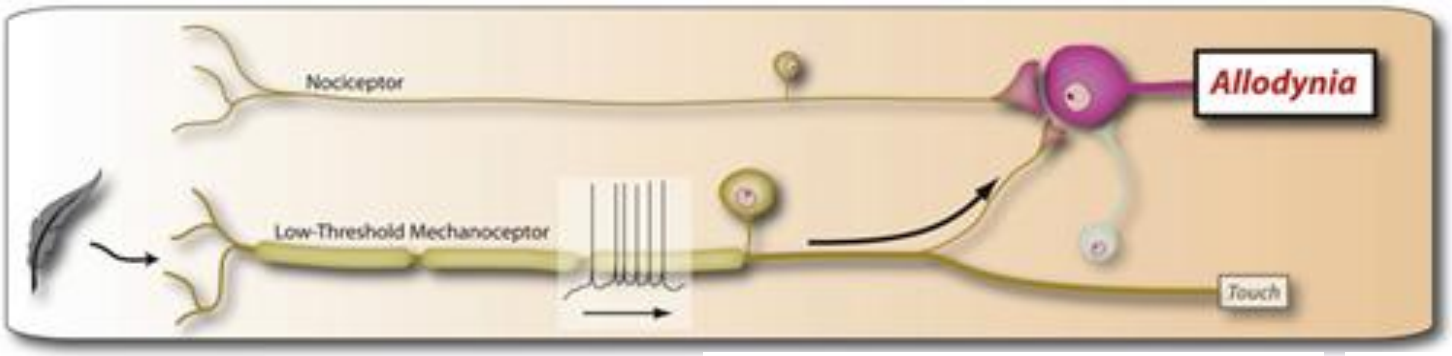


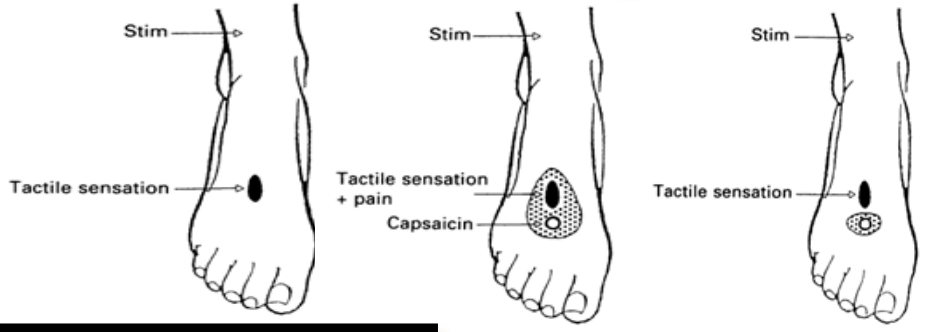
Typically a burning, tender sensation during soft stroking of the affected skin

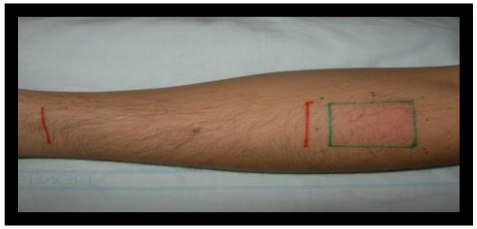
CT optimal stroking has similarities to that which evokes tactile allodynia

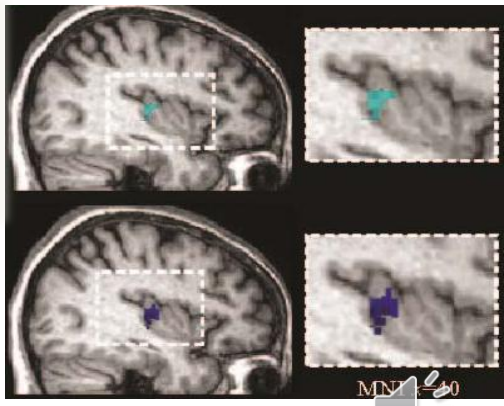
Does CT touch paradoxically cause allodynia?

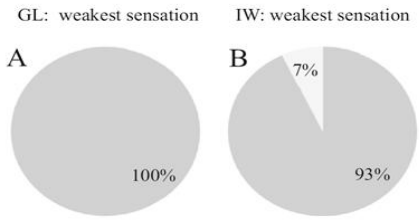


- Canonical view
  - Allodynia due to rerouting of A-beta touch inputs in the spinal cord dorsal horn
- Emerging view
  - A-beta nerve block
  - Sensory testing and neuroimaging in patients lacking A-beta fibres
  - CT afferents play a role









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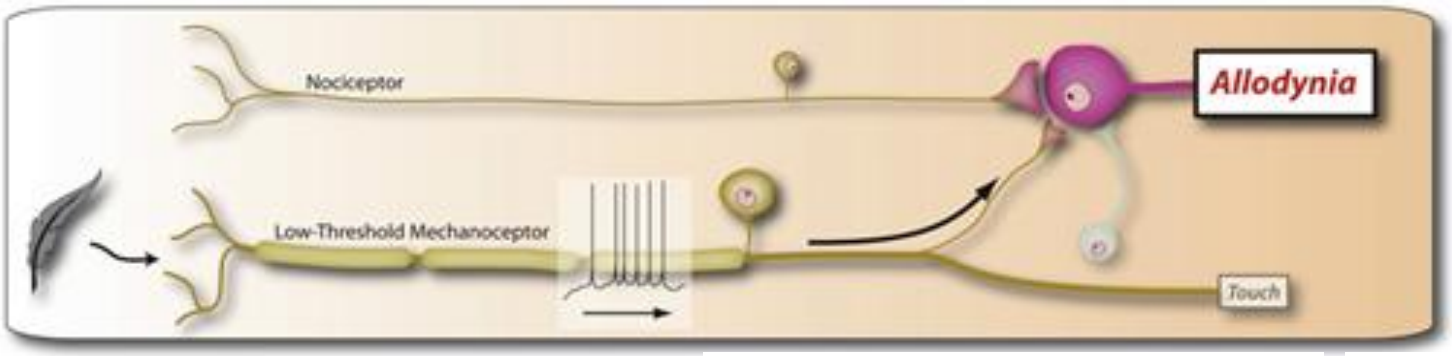

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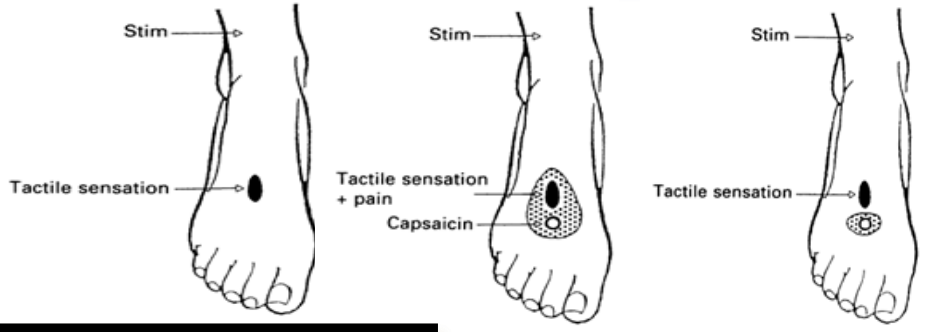
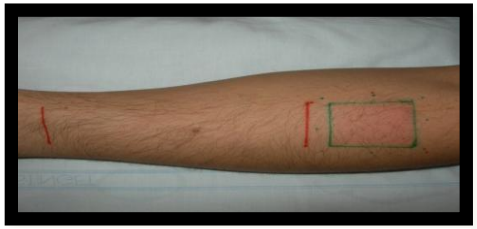
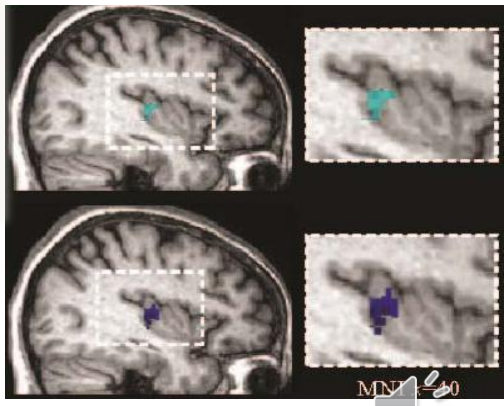
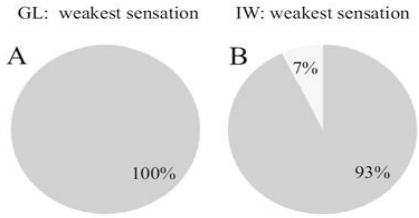
- Emerging view
  - A-beta nerve block
  - Sensory testing and neuroimaging in patients lacking A-beta fibres
  - CT afferents play a role
  - **<u>Need a model of CT afferent block</u>**



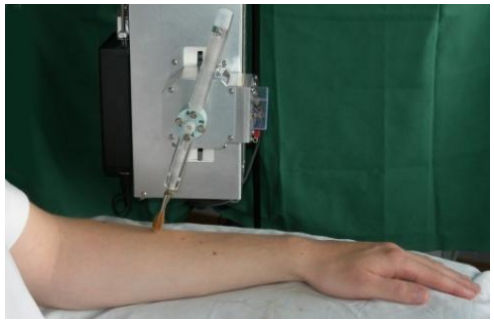


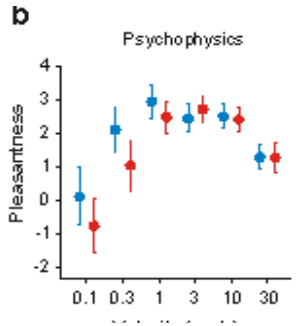




Developing a model to evaluate C-Tactile fibre contribution to allodynia and for testing new topical Medications – a microneurography and psychophysical study

- Aim to differentially block CT afferents using non-invasive delivery of Lidocaine
- Part 1
  - Quantitative Sensory Testing
    - 20 participants
    - Control versus Lidocaine
    - Iontophoresis





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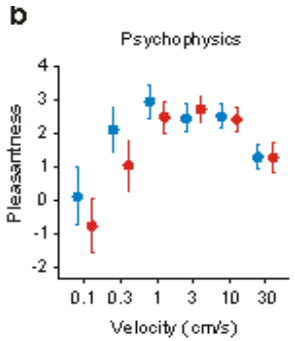
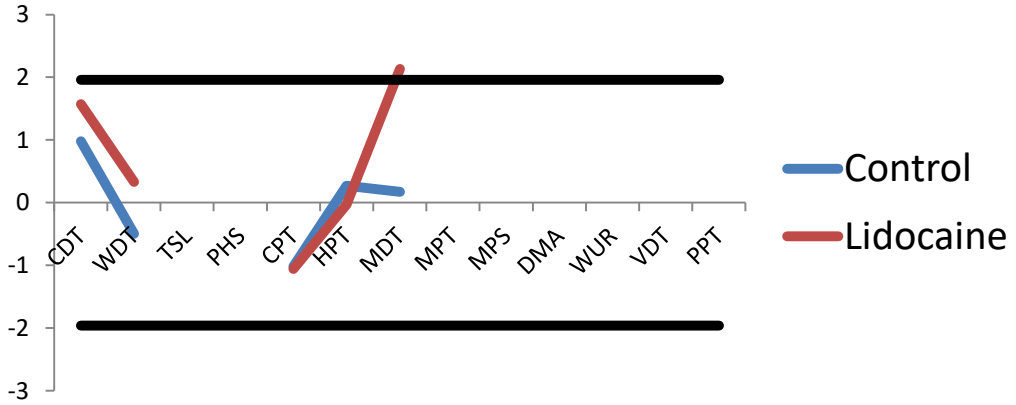
- Aim to differentially block CT afferents using non-invasive delivery of Lidocaine
  - Quantitative Sensory Testing
    - Elevated mechanical detection threshold
    - CT touch not altered





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Developing a model to evaluate C-Tactile fibre contribution to allodynia and for testing new topical Medications – a microneurography and psychophysical study

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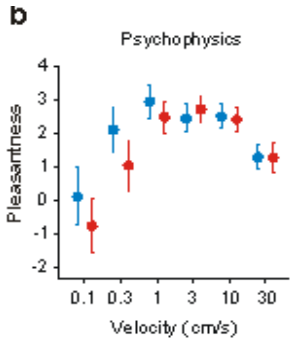
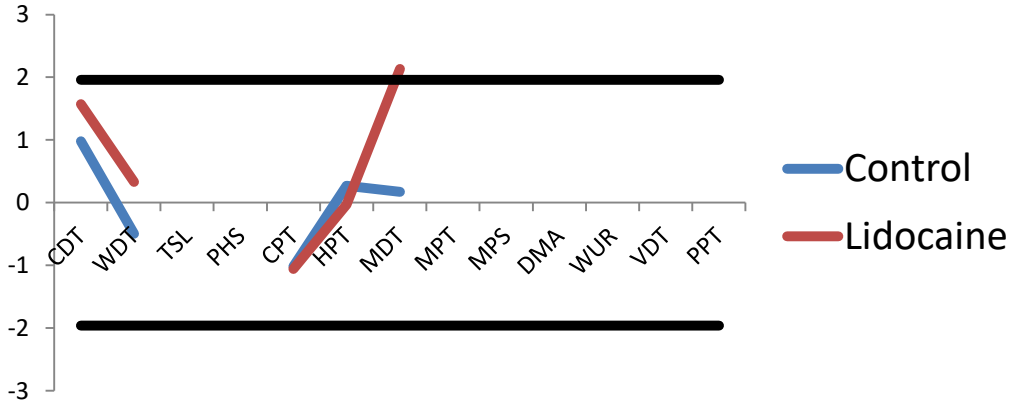
  - Quantitative Sensory Testing
    - Elevated mechanical detection threshold
    - CT touch not altered
- Suggests not pure CT afferent blockade





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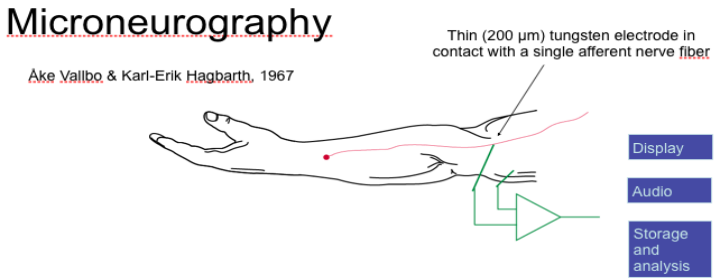
- Aim to differentially block CT afferents using non-invasive delivery of Lidocaine
- Part 2
  - Microneurography
  - To confirm inferences of QST
    - 35 experiments
    - High failure rate initially



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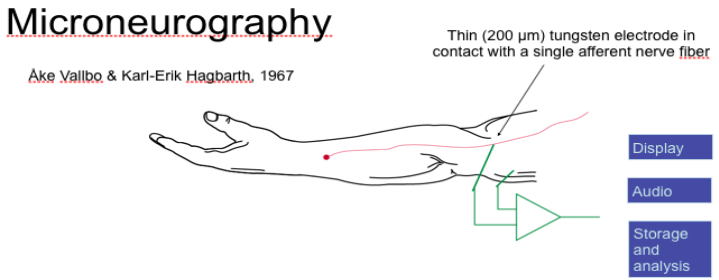
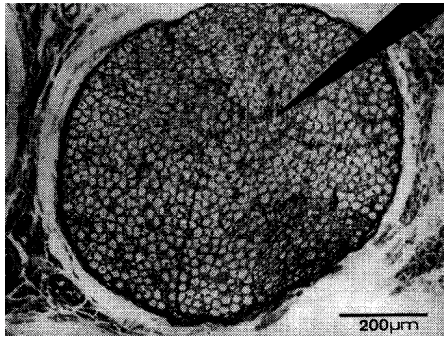
  - To confirm inferences of QST
    - 30-40 experiments
    - High failure rate initially





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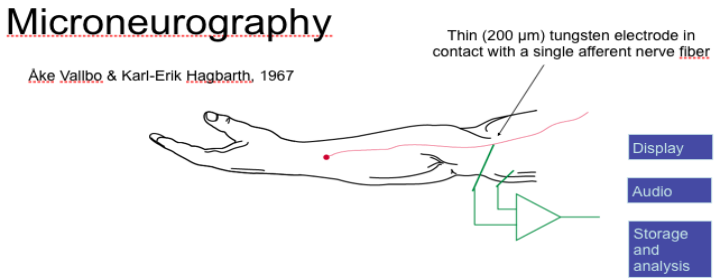
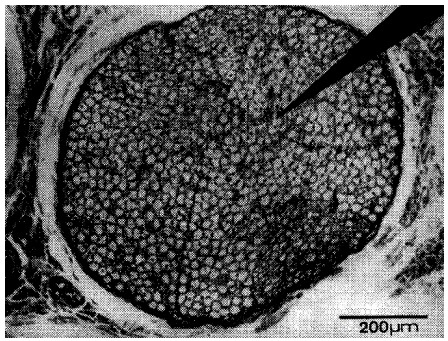
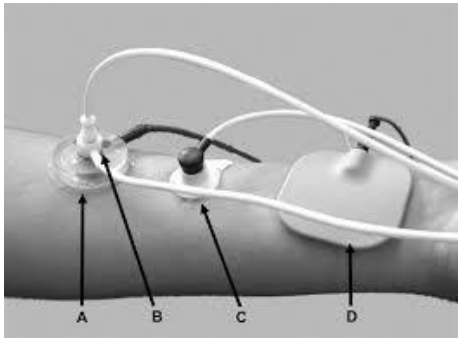
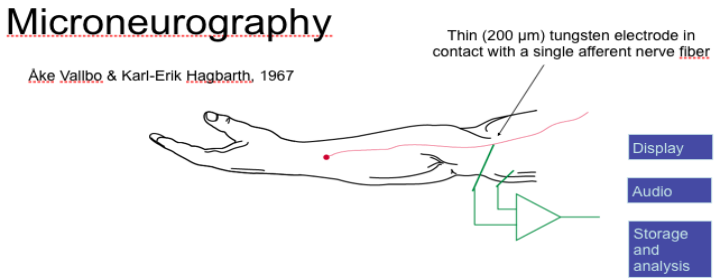


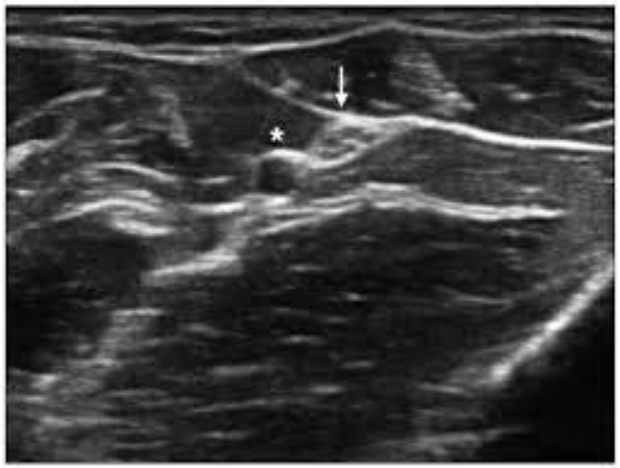




Developing a model to evaluate C-Tactile fibre contribution to allodynia and for testing new topical Medications – a microneurography and psychophysical study

- Aim to differentially block CT afferents using non-invasive delivery of Lidocaine
- Part 2
  - Microneurography
  - To confirm inferences of QST
    - 30-40 experiments
    - High failure rate initially





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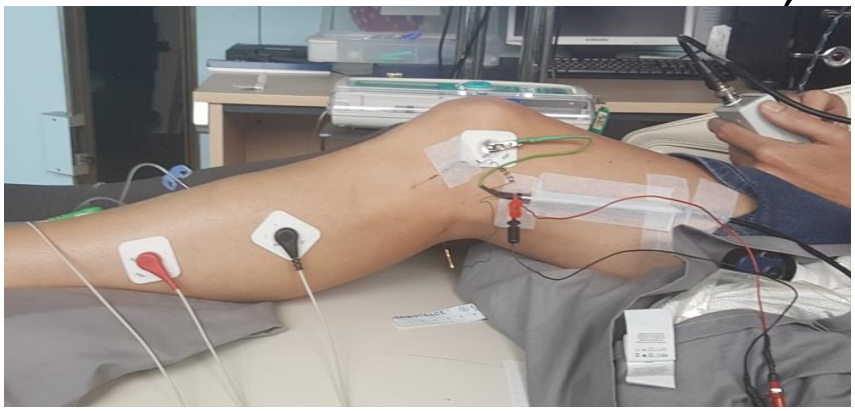
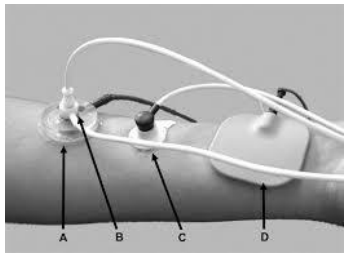
Pharmaco-microneurography

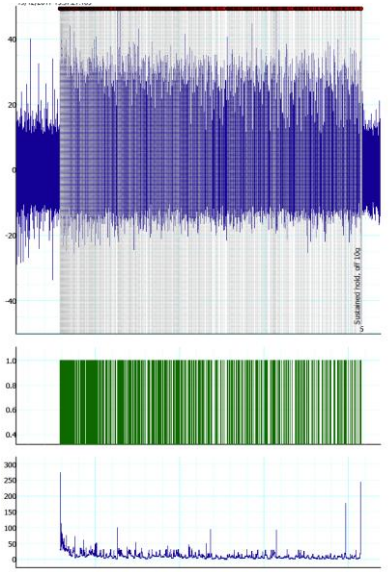
- Iontophoresis experiments
  - Lidocaine +/- adrenaline into unit receptive field
  - Most touch fibre types unaffected, some still to be analysed
    - Hair Follicle Afferents, Field Units, SA2





SA1 Fibre

Pre-lidocaine



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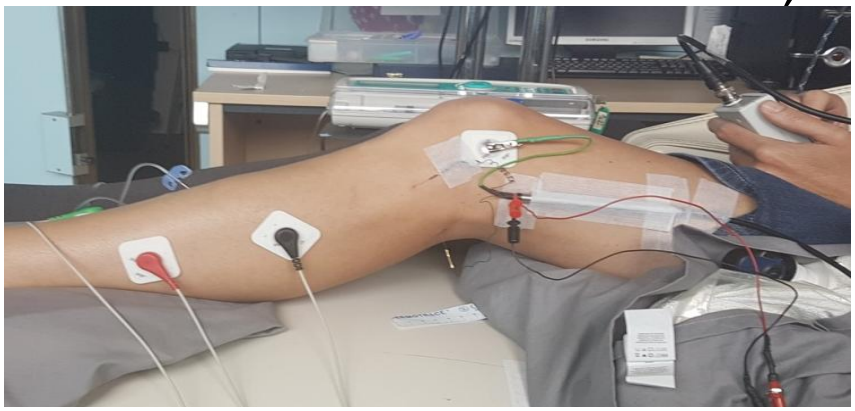
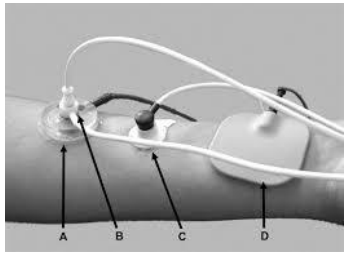
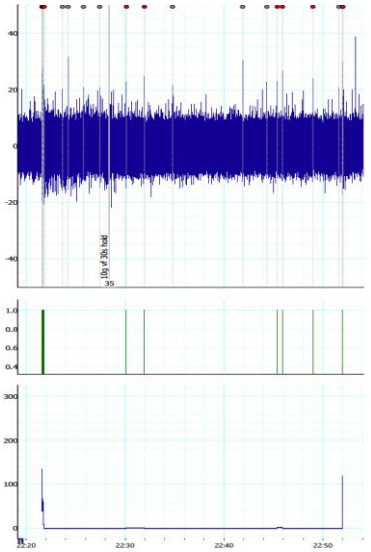




SA1 Fibre

Post-lidocaine



Pharmaco-microneurography

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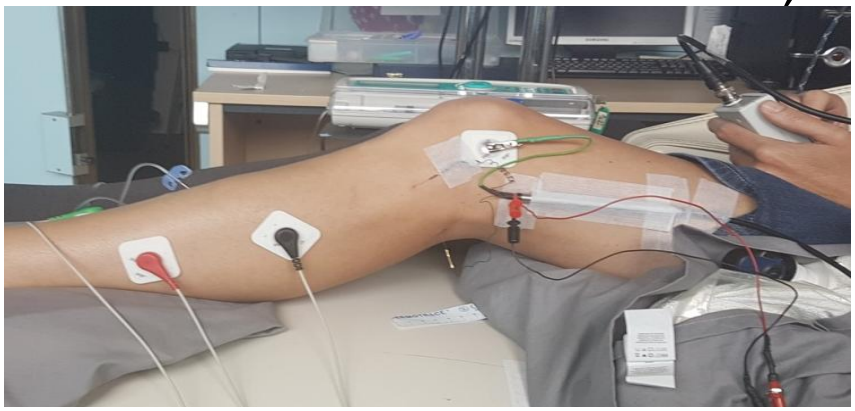

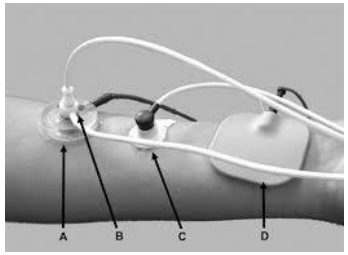

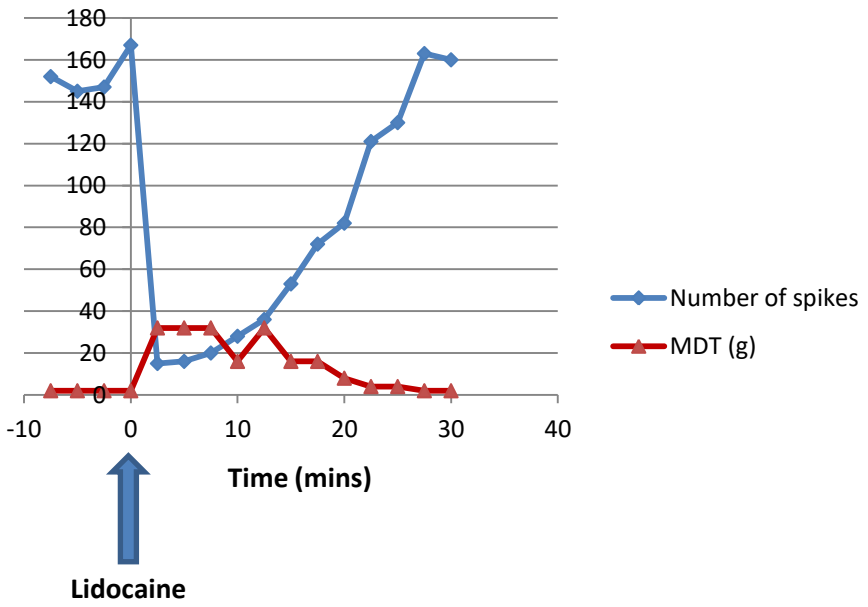

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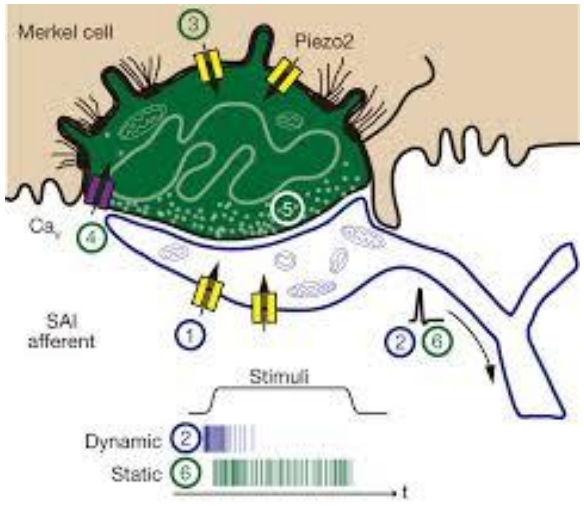
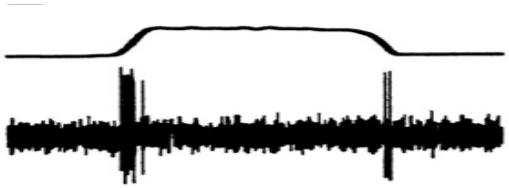


Pre-lidocaine

Post-lidocaine

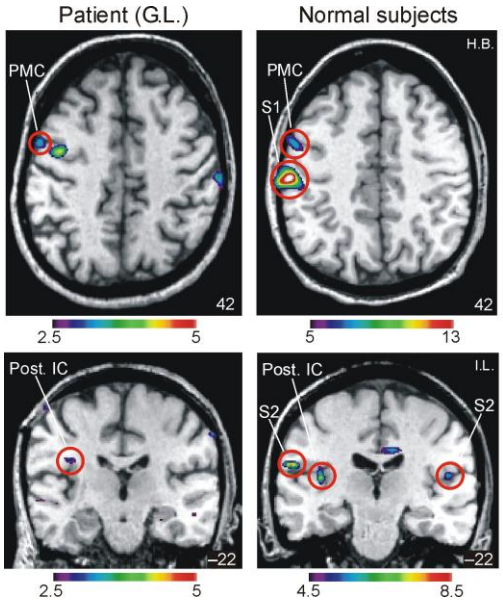


-Previously suggested that ‘Blocking Piezo 2 is a candidate for treating Allodynia’

- Opportunity for other agents / ligands…

‘Investigating the second order spinal projection pathway of C-Tactile afferents and their contribution to pain processing.’

- **C-Tactile pathways**
  - Peripheral nerve
    - C-fibre
  - Cortical targets
    - Dorsal Posterior Insula Cortex
    - Brain region also important for pain processing



Olausson et al, Nature Neurosci 2002, 5, 900-4

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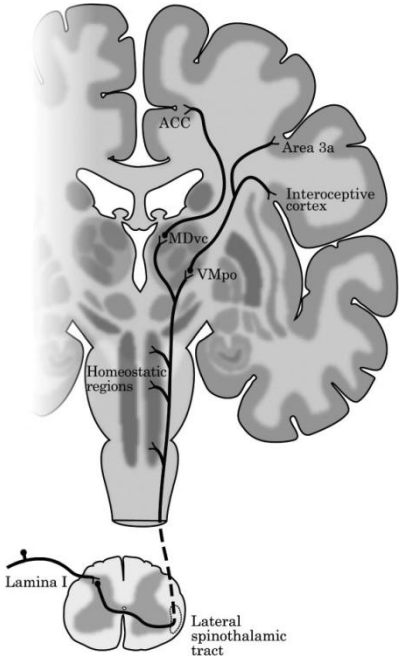
‘Investigating the second order spinal projection pathway of C-Tactile afferents and their contribution to pain processing.’

- **C-Tactile pathways**
  - Peripheral nerve
  - Cortical targets
  - Spinal pathway unknown
    - **All available evidence suggests that CT afferents should project alongside ‘pain’ fibres in the ‘spinothalamic tract’**



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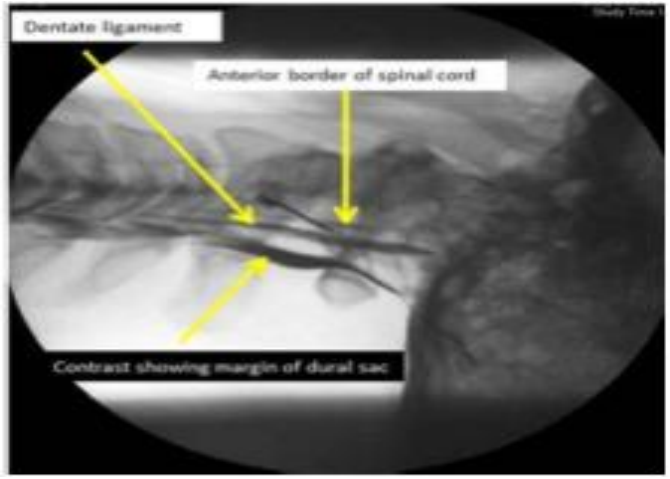
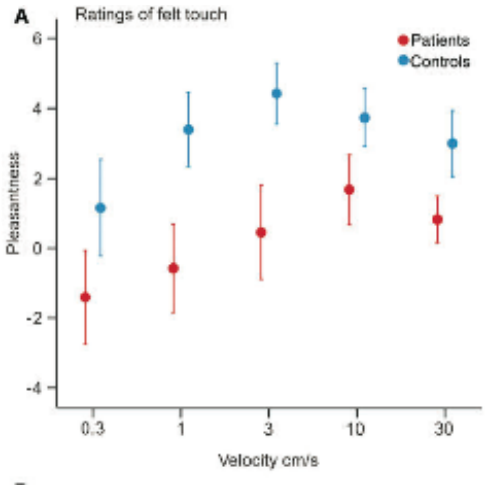
‘Investigating the second order spinal projection pathway of C-Tactile afferents and their contribution to pain processing.’

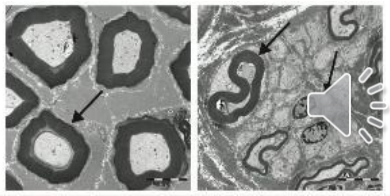


- Anterolateral C1/C2 cordotomy under light sedation **(Manohar Sharma)**
- Hypothesis: Cordotomy will disrupt CT pathways
- Psychophysics

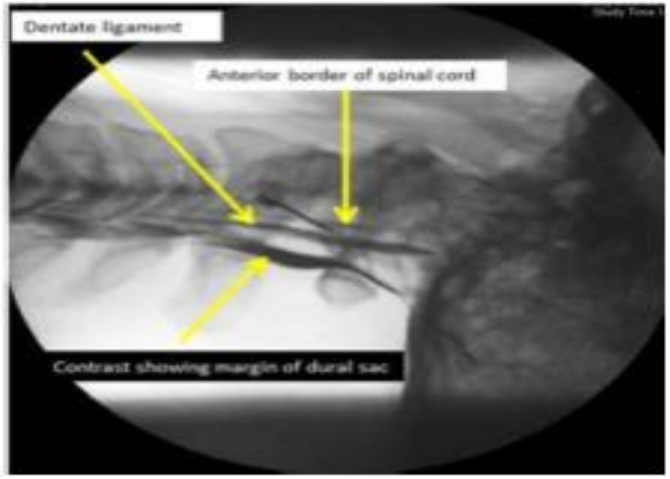
- Total/sub-total loss of cold/warm sensation, itch and pain contralateral to cordotomy



HSAN-V



‘Investigating the second order spinal projection pathway of C-Tactile afferents and their contribution to pain processing.’



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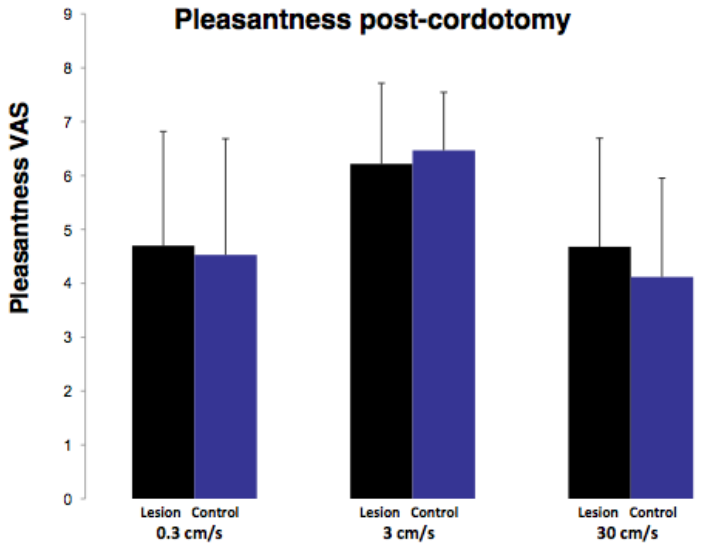
- Hypothesis: Cordotomy will disrupt CT pathways
- Psychophysics

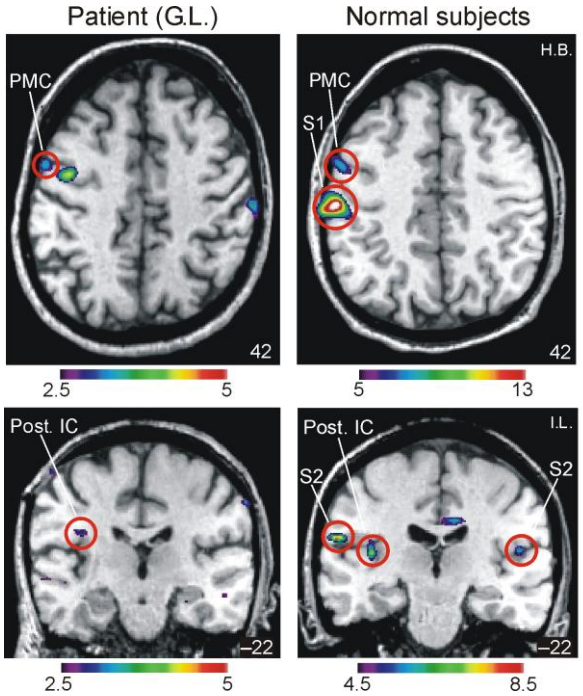
- Total/sub-total loss of cold/warm sensation, itch and pain contralateral to cordotomy
- **<u>No change in measures of pleasant touch</u>**
- Stroking felt as less intense



Created a bit of a puzzle…

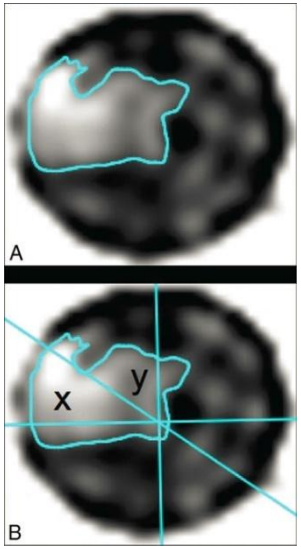
- Incomplete interruption of spinothalamic tract?
- CT pathway has been interrupted and patients are relying on A-beta touch fibres?
- There is a different pathway?
- The spinal cord is not just a passive conduit
  - Processing and integration of A-beta, CT and noxious range (i.e. ‘pain’) touch fibres
- **Requires somatosensory mapping and physiological testing**

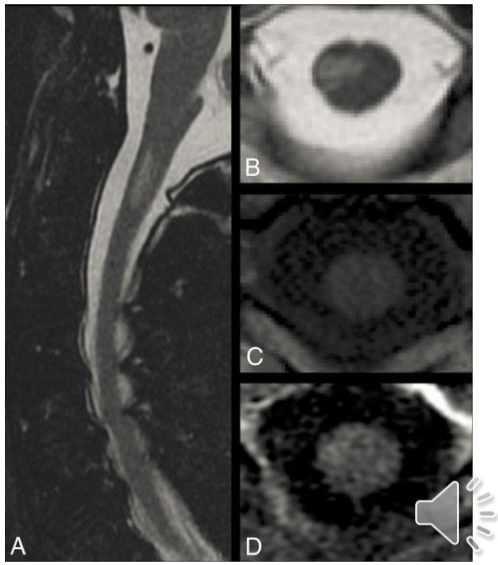
‘Investigating the second order spinal projection pathway of C-Tactile afferents and their contribution to pain processing.’



- Spinal and Brain imaging
  - Volumetric
  - Brain fMRI
  - DTI
- Psychophysiology (GSR, HRV)

- Anterolateral C1/C2 cordotomy under light sedation
- Psychophysics
- C-Tactile function and Pain





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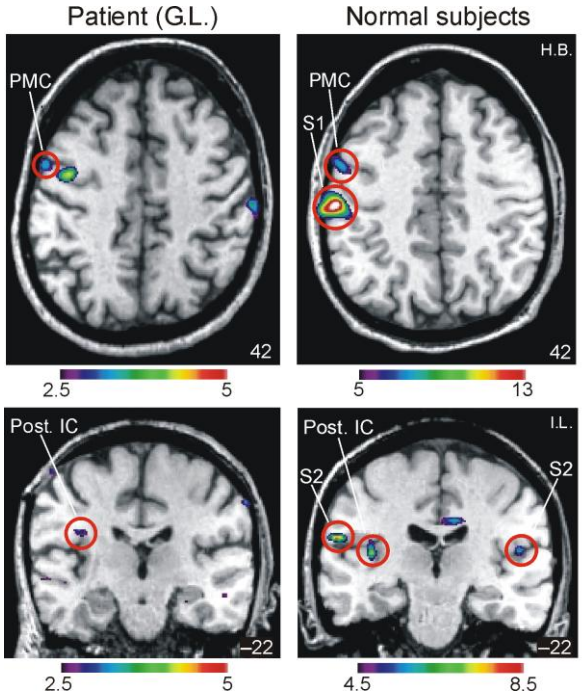

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  - Brain fMRI
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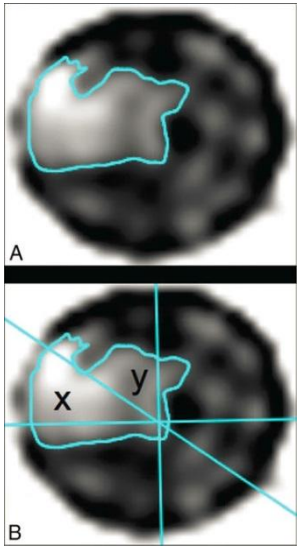
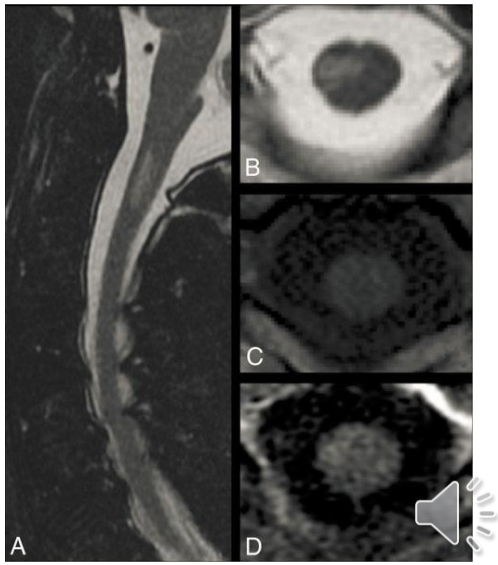
Hypothesis: CT fibres travel with ‘pain’ fibres and will be disrupted by cordotomy. CT touch will result in...

- Less activation of DPIns
- Attenuated heart rate deceleration

- Compare Right and Left
- Compare with painful mechanical stimulation





Thank you!