The Curse Of Soft Touch

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• 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, SAI, RA)
  - vibration (Pacinian, Pc)
  - hair movements (Hair afferents)
**Thin myelinated (Ad)**
- ~5-35 m/s
- Temperature: cold
- Pain, Touch?

**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)

Fast and slow touch
How to Study C-Tactile Fibres

Psychophysics

Löken et al., Nature Neuroscience 2009
Thin (200 μm) tungsten electrode in contact with a single afferent nerve fiber.
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.

Löken et al., Nature Neuroscience 2009
Pharmacogenetic activation of Mrgprb4-expressing neurons in freely behaving mice promoted positively reinforcing and/or anxiolytic behaviour.

Pain modulatory role of C-LTMRs

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

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

Slow brush stimulation reduces adult pain
Liljencrantz et al 2017

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

Slow brush stimulation reduces adult pain
Liljencrantz et al 2017
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**

![Images of mechanical testing with Q-tip, cotton wool, and soft brush]

- **Tactile Allodynia**
  - Pain score (log10)
  - Q-tip, Cotton wool, Soft brush
  - Clinical vs Control

- **Mechanical Hyperalgesia**
  - Pain score (log10)
  - Mechanical Pinprick (mN)
  - Clinical vs Control
'makes its victim ward off his daughters embrace 'as though it were an enemy's blow'
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.

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
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
  - **Need a model of CT afferent block**
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
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
  - Quantitative Sensory Testing
    - Elevated mechanical detection threshold
    - CT touch not altered
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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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• Part 2
  – Microneurography
  – To confirm inferences of QST
    • 35 experiments
    • High failure rate initially
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    • 30-40 experiments
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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

![Pre-lidocaine](image1)

SA1 Fibre

![Post-lidocaine](image2)
Pharmaco-microneurography

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• Hair Follicle Afferents, Field Units, SA2
Pharmaco-microneurography

• Iontophoresis experiments
  – Lidocaine +/- adrenaline into unit receptive field

- 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*
‘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’
‘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
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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
• **No change in measures of pleasant touch**
• Stroking felt as less intense

![Contrast showing margin of dural sac](image)
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.’

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

- Spinal and Brain imaging
  - Volumetric
  - Brain fMRI
  - DTI
- Psychophysiology (GSR, HRV)
‘Investigating the second order spinal projection pathway of C-Tactile afferents and their contribution to pain processing.’

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

• Spinal and Brain imaging
  • Volumetric
  • Brain fMRI
  • DTI
• Psychophysiology (GSR, HRV)
Thank you!