Chronic Pain Syndromes and Central Pain Mechanisms

Dr Helen Cohen
Consultant – Rheumatology & Chronic Pain, Royal National Orthopaedic Hospital

Measuring Pain

• Pain: Sensation AND perception

• The problem of qualia (is what I call ‘green’ the same as what you see as ‘green’?)
The Problem of Chronic Pain

Chronic pain is the leading cause of disability in the United States (Centers for Disease Control and Prevention).

Osteoarthritis: 20 million people (NIAMS); more than 16 million people (NWHIC)

Rheumatoid arthritis: 2.5 million Americans (NWHIC); 1% of US population (NIAMS)

NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NWHIC: The National Women's Health Information Center
Chronic Pain Conditions

- Arthritis
- Cancer
- Neuropathic

- **Pain disproportionate to injury or in absence of injury**
  - Chronic fatigue syndrome / ME, IBS, chronic interstitial cystitis, chronic pelvic pain, temporomandibular joint dysfunction etc

Chronic Pain in Rheumatic Disease

- Inflammatory: trauma, auto-immune
- Non-inflammatory: Osteoarthritis (OA ?)

**Pain disproportionate to injury or in absence of injury**

Fibromyalgia, repetitive strain injury, failed back surgery, Complex Regional Pain Syndrome (CRPS), hypermobility (HMS)

**Overlap:** With other pain syndromes
  - With ‘inflammatory’ rheumatology
Contributing Factors

Sensitisation of peripheral and central nervous systems

Peripheral sensitisation

- Peripheral sensitization is a reduction in threshold and an increase in responsiveness of the peripheral ends of nociceptors though peripheral nerves to the central nervous system.

- Previously ‘silent’ c-fibres become active
Central sensitisation

• Central sensitization is an increase in the excitability of neurons within the central nervous system, so that normal inputs begin to produce abnormal responses.

Genetic Factors

• There is inter-individual variation in
  – Pain sensitivity
  – Analgesic response
  – Susceptibility to painful pathology
Other mechanisms

- Neurogenic inflammation
- Gender
- Exaggerated inflammatory response, protective disuse, myofascial dysfunctions
- Sympathetically maintained pain

Central Processing

- Chronic pain as a network dysfunction
- No single ‘pain centre’
- Somatotopic maps S1, S2, & beyond
- Many brain areas can be activated (fMRI: consistently spinal cord, thalamus, S1, S2, insula, anterior cingulate and prefrontal cortex ALSO hippocampus, posterior parietal lobe, basal ganglia and brainstem)
Pain network

- fMRI study brush evoked allodynia in neuropathic pain patients (Schweinhardt 2006)
Cortical remapping following hand amputation and 5 months post transplantation.

Pre-surgery  
Immediately post-surgery  
Following hand transplantation  
5 months later  

Farné A et al 2002
Referred Sensations

In amputees:

Halligan PW et al. BMJ 1999

In CRPS:

McCabe et al. Rheumatology 2003

Pain is an emotion and a sensation

AFFECTIVE

Amygdala
hypothalamus

attention

Parabrachial

SENSORY

Somatosensory
cortex

Thalamus

Skin

A-delta
C-fibre

Painful
stimulus

Spinal Cord

Lamina I

Substance P
glutamate

Lamina V

Thanks to Tony Dickenson for these slides!
Chronic pain syndrome overlaps

Poor response to analgesics

Overlapping mechanisms?

In fibromyalgia

Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study. Staud R, Nagel S, Robinson ME, Price DD. Pain. 2009 Sep;145(1-2):


## fMRI in fibromyalgia

**Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with fibromyalgia.**


**Fibromyalgia unique temporal brain activation during experimental pain: a controlled fMRI Study.**


**White and gray matter abnormalities in the brain of patients with fibromyalgia: a diffusion-tensor and volumetric imaging study.**


**Variations in brain volume and regional morphology associated with chronic pain.**


---

![fMRI Image](image_url)
Remapping in FMS

CORTICAL REORGANISATION AND CHRONIC PAIN: IMPLICATIONS FOR REHABILITATION

Herta Flor

From the Department of Clinical and Cognitive Neurosciences, University of Heidelberg, Clinic for Internal Medicine, Mannheim, Germany

Includes fibromyalgia

Referred Sensations in FMS?

Contribution of the local and referred pain from active myofascial trigger points in fibromyalgia syndrome.

CRPS: Why the interest?  
What’s the relevance?

• Pathogenesis?  
  Can occur without trauma  
  CENTRAL pain mechanisms in chronic pain (ie ‘the brain’)

• Autonomic nervous system (ANS) involvement  
  ANS / central NS cross talk?

• Patient characteristics  
  Allodynia  
  Poor response to pain killers  
  Overlap with other ‘functional’ pain syndromes  
  – FMS, CFS, HMS

Other features in CRPS

• Distorted body image  
• Clumsiness/lack of control  
• Poor balance/proprioception  
• Sensory sensitivity eg. Noise, light
Body perception

Phantom limbs in amputees

- Altered in CRPS
  - Foreignness
  - Dysmorphia
  - ‘phantom swelling’
In FMS?

• Phantom swelling of limbs

Sympathetically maintained pain in CRPS

- Swelling
- Sweating
- Colour
- Temperature
- Allodynia
Thermography

In CRPS

Sympathetic autonomic vasomotor/sudomotor disturbance

Sympathetic dysfunction in FMS

Fibromyalgia as a sympathetically maintained pain syndrome.
Martinez-Lavin M.

Abnormal sympathovagal balance in men with fibromyalgia.
Cohen H, Neumann L, Alhosshle A, Kotler M, Abu-Shakra M, Buskila D.

Dysautonomia, fibromyalgia and reflex dystrophy
Jean Eisinger

Unit Infranalgies, Centre Hospitalier, 83156 Toulon, France

Corresponding author: Jean Eisinger, infranalgies@wanadoo.fr

Published: 6 July 2007

Hypermobility

- Autonomic dysfunction – orthostatic intolerance, Postural Orthostatic Tachycardia Syndrome (PoTS), GI hypomobility, bladder instability
- Poor proprioception / balance
- Sensory sensitivity
- STRONG overlap with FMS, CFS

Proprioception

CRPS, hypermobility & fibromyalgia?

- Don’t always know where the limbs are
- ‘Clumsiness’
- May contribute to falls.
- Formal neurological testing is normal.

Failure of integration
Sensory Integration Dysfunction
‘Sensory Defensiveness’

- ‘a neural processing disorder affecting modulation of sensory input which triggers an inappropriate response to an otherwise harmless stimulus’
- More common in children with learning disorders (attention deficit disorder, autism, fragile X syndrome)
- Recognised in adults (constitutional and acquired through brain trauma).
- Exaggerated responses to sensory stimuli (eg. tactile, auditory, olfactory etc.) that most other people perceive as benign.
- There are a number of hypotheses of sensory integrative dysfunction and most require an element of neuroplasticity.

Why don’t drugs seem to work?

Causes of chronic pain – largely unknown
It is suggested that:

- Multiple mechanisms involving various regions of entire neuraxis

- Pathophysiology may vary from one patient to another
Treatment: drugs

- Keep it simple
- WHO pain ladder – BUT
- Opiates – pain is often poorly responsive, escalating doses, addiction/tolerance, side effects – bladder, bowel, memory, attention, personality
- Neuromodulatory – anticonvulsant, antidepressant

Treatment: drugs

- Nocturnal pain – amitriptyline, nortriptyline
- Slow release formulations
- Patches
- Neuropathic pain: Gabapentin, pregabalin – NB. weight gain
### Fibromyalgia

- Amitriptyline superior to D, M for pain, sleep, fatigue
- Duloxetine – superior to M for sleep disturbance, pain
- Milnacipran – superior to D for fatigue
- Pregabalin
- Sodium Oxybate (trade name Xyrem) = γ-Hydroxybutyric acid (GHB)’/’GBH’
- None are licensed in the UK for FMS

**Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. Häuser W, Petzke F, Üçeyler N, Sommer C. Rheumatology. 2011 Mar;50(3):532-43.**

### Non-pharmacologic

- Graded exercise programme
- Pain management approach
- Multidisciplinary team
- Out-patient vs In-patient
- eg. Out patient FMS coping skills programme RNHRD, COPE pain management programme NHNN
- In patient PMP eg. RNOH, RNHRD
- Back school eg. ‘active back programme’ at RNOH
- Long term self-management strategies
- Patient education
- Support groups/ expert patient programme
Treatment summary

• Some patients: Relief at acknowledgement of pain, learn how to control symptoms. Minimal medication, out-patient based input.

• Others: Pain focussed, polypharmacy, marked physical deconditioning (wheelchair, crutches), psychological issues – PMP approach

• *Differentiate inflammatory from non-inflammatory pain

So you don’t believe all this brain stuff….
Thanks for listening…
The motor control system

Conflicting sensory information

- May cause pain (Harris)
- Cortical reorganisation as a cause
- Can cause pain in healthy volunteers
- Can worsen pain in FMS

Simulating sensory–motor incongruence in healthy volunteers: implications for a cortical model of pain

- Twenty-seven subjects (66%) reported at least one anomalous sensory symptom at some stage in the protocol

Somaesthetic disturbances in fibromyalgia are exaggerated by sensory–motor conflict: implications for chronicity of the disease?

- Twenty-six subjects (89.7%) with FMS reported changes in sensory perception at some stage in the protocol.
Extinction

- Motor and sensory
- Motor with mirror: only observed limb moves
- Sensory: bilateral touch felt unilaterally
- Described in stroke
- Both seen in CRPS
- Observed in FMS using mirror