# Too Hot To Handle

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TNRG Therapeutic Neuroscience Research Group

EIM Evidence in Motion

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## Disclaimer...

- Many VERY smart people have contributed to this
- I am "dumbing it down" so I can understand it
- Will all neuroscientists, neurobiologists and immunologists please leave…
- A LOT remains unknown about CRPS…

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## A Neuroscience CRPS definition...

**CRPS is a multiple system output, activated by the pain neuromatrix (brain map) in response to perceived threat**

Adapted from Moseley GL. A pain neuromatrix approach to patients with chronic pain. *Man Ther.* Aug 2003;8(3):130-140.

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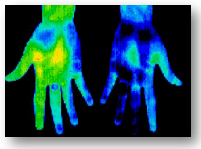
## Introduction: CRPS



- **Pain in combination with sensory, autonomic, trophic and motor abnormalities.**
  - **CRPS-1: Nerve lesion cannot be identified**
  - **CRPS-2: Nerve lesion can be identified**

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## Introduction

- **Criticism of CRPS 1 and CRPS 2**
  - Fracture or surgery - damage peripheral nerve, but usually Dx as CRPS 1
  - **Nerve degeneration causes CRPS-1?**
    - Other causes of neuropathic pain are frequently associated with a loss of C-fiber peripheral terminals, the specificity of these findings with respect to CRPS is questionable (Devigili).

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## Introduction

- Our understanding of CRPS has increased substantially in the past decade.
- **Three major pathophysiological pathways:**
  1. Aberrant inflammatory mechanisms
  2. Vasomotor dysfunction
  3. Maladaptive neuroplasticity.
- Between-individual variability

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## Clinical presentation & diagnosis

## Clinical presentation & diagnosis

- After minor or moderate tissue injury (i.e., a wrist fracture).
- In the acute phase, the injured limb is usually extremely painful, red, warm (although sometimes it quickly becomes cold) and swollen (Veldman 1993).



## Clinical presentation & diagnosis

- Allodynia (non-painful stimuli evoke pain)
- Hyperalgesia (painful stimuli evoke more intense pain than usual)
- Changes in sweating
- Changes in hair and nail growth
- Muscle weakness
- Mechanical and thermal hyperalgesia are frequently present

## Clinical presentation & diagnosis

- Pain often spreads
- Voluntary motor control is reduced
- Hyperpathia (nociceptive stimuli evoke exaggerated levels of pain)
- Negative sensory signs
  - Hypoesthesia (reduced sense of touch)
  - Hypoalgesia (decreased sensitivity to painful stimuli)
  - Hypothermesthesia (abnormally decreased sensitivity to heat)

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## Clinical presentation & diagnosis

- Mixture of noxious sensations and sensory loss
- Over months: Warm limb becomes cold
- Dystonia
- Tremor
- Myoclonus
- Activity of the limb: exacerbates signs and symptoms
- Over time, clinical features spread proximally (but not distally) and can even emerge on the opposite or ipsilateral limb

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## Clinical presentation & diagnosis

- **Diagnosis of CRPS:**
  - Orlando criteria
  - International Association for the Study of Pain
  - Modified version called the Budapest criteria (panel)
  - Diagnosis according to the Budapest criteria - grouping of signs and symptoms into four distinct categories

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## Diagnosis: Budapest Criteria

**Panel: Budapest diagnostic criteria for CRPS** (Harden, Bruehl et al. 2010)

1. Continuing pain, which is disproportionate to any inciting event

2. Must report at least one symptom in three (clinical diagnostic criteria) or four (research diagnostic criteria) of the following categories:
   - Sensory: hyperesthesia or allodynia
   - Vasomotor: temperature asymmetry, skin color changes, or skin color asymmetry
   - Sudomotor or edema: edema, sweating changes, or sweating asymmetry
   - Motor or trophic: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)



## Diagnosis: Budapest Criteria

3. Must display at least one sign at time of diagnosis in two or more of the following categories:
   - Sensory: hyperalgesia (to pinprick) or allodynia (to light touch, deep somatic
   - pressure, or joint movement)
   - Vasomotor: temperature asymmetry, skin color changes or asymmetry
   - Sudomotor or edema: edema, sweating changes, or sweating asymmetry
   - Motor or trophic: decreased range of motion, or motor dysfunction (weakness,
   - tremor, or dystonia), or trophic changes (hair, nails, or skin)

4. No other diagnosis better explains the signs and symptoms



## Epidemiology

- **Unclear**
  - 5 cases per 100,000 person-years in the USA
  - 26 per 100,000 person-years in the Netherlands.
  - Might expect that 20,000–80,000 new cases of CRPS would be identified per year in the USA.
- Incidence increases with age until 70 years of age, and 3–4 times more women than men are affected.
- The arm is affected in about 60% of cases and the leg in about 40%.

## Epidemiology

- **Resolution rate:**
  - Ranging from 74% in the first year to 36% within 6 years.


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## Epidemiology

- Fractures (about 45%), sprain (about 18%), and elective surgery (about 12%) are the most frequently reported triggering events.

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## Epidemiology

- **Spontaneous-onset CRPS** - uncommon (<10% of cases).
- Associated with substantial disability, loss of quality of life, and personal and societal economic burden.

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## Risk factors & prognostic determinants

- **Lots of people have fractures, injuries and surgery and DO NOT develop CRPS**
- Some individuals are more susceptible than others.


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## Risk factors & prognostic determinants

1. **Psychological factors**
2. **Immobilization of injured limb**
3. **Epidemiological factors**
4. **Genetic factors**


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## 1. Psychological risk factors

- Compelling evidence that patients with CRPS are more **anxious** and **depressed** than healthy control individuals.
- Whether patients with CRPS are **more anxious** and **depressed** than patients with other chronic pain syndromes is unclear

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## ~~1. Psychological factors~~


- **No evidence of psychological risk factors for CRPS onset**
  - A large population-based case control study reported no difference in psychological variables between those who developed CRPS after trauma
  - Recent prospective multi center cohort study - 600 consecutive patients with a fracture reported that none of the psychological factors predicted the development of CRPS-1.
- The popular presumption that anxiety and depression predispose to CRPS is incorrect.

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## 2. Immobilization of the injured limb

- **Immobilization - risk factor for CRPS.**
- Topical application of capsaicin (induces neurogenic inflammation):
  - Mechano sensitivity
  - Thermo sensitivity,
  - Perceptual disturbances

  reported in people whose limb was subsequently immobilized for 24 h, but not in people whose limb was not immobilized (Moseley GL, unpublished).
- The signs rapidly resolved once the limb was moved again.

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## 3. Epidemiological findings

- Angiotensin-converting-enzyme inhibitors at the time of trauma and a history of **migraine** or asthma - associated with increased risk of developing CRPS.
- **Migraine** - risk factor for CRPS
  - Both of these risk factors implicate inflammation: angiotensin-converting-enzyme inhibitors increase the availability of **substance P** and **bradykinin**, which are important mediators of inflammation, and migraine and asthma share an underlying mechanism of **neurogenic inflammation** with CRPS.

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## 3. Epidemiological findings

- Fracture - more favorable course than soft tissue injury
- Gender does not seem to affect prognosis
- Women > men: risk for more severe form of CRPS
- Cold CRPS: Worse prognosis than warm CRPS

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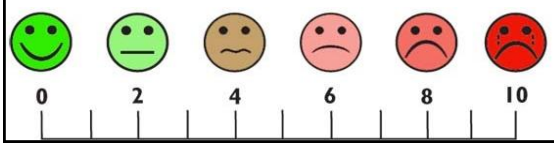
## 3. Epidemiological findings

- **Longitudinal study**
  - 1549 nearly consecutive patients who presented with wrist fracture and who were managed non-surgically were assessed within 1 week of their fracture and then followed up 4 months later (Moseley GL, unpublished).
- **Mean pain intensity over the past 2 days (> 5/10): Red flag for CRPS**




## 4. Genetic findings

- CRPS sometimes occurs in several family members and siblings of young-onset cases have an increased risk of developing the syndrome
  - Suggest potential genetic predisposition to CRPS
  - Need more research

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## Genetics?

Genetically Coded…

Environmentally Sculpted

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## Risk factors & prognostic determinants summary…

1. Anxiety/depression – no
2. Immobilization after fracture – yes
3. Neurogenic inflammation – yes
4. High level of acute pain – yes
5. Genetics – likely
6. Gender, fracture, etc. – not compelling


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## Before we move on…

A neuroscience explanation of these risk factors is needed to start the understanding the **vast neurobiological and neurophysiological processes** that underpin the development and maintenance of CRPS…

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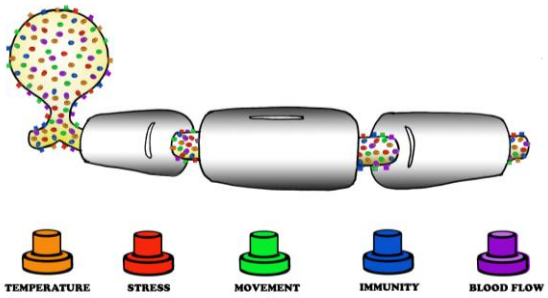
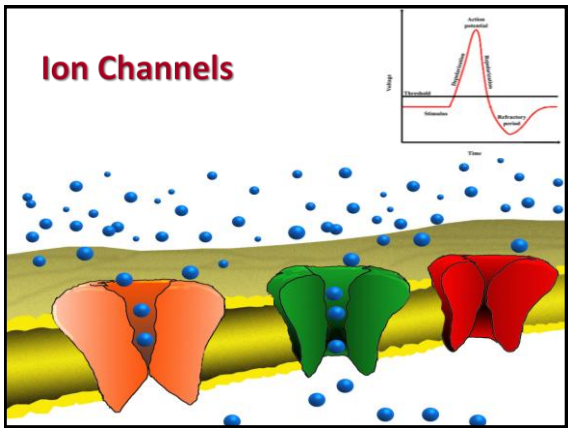
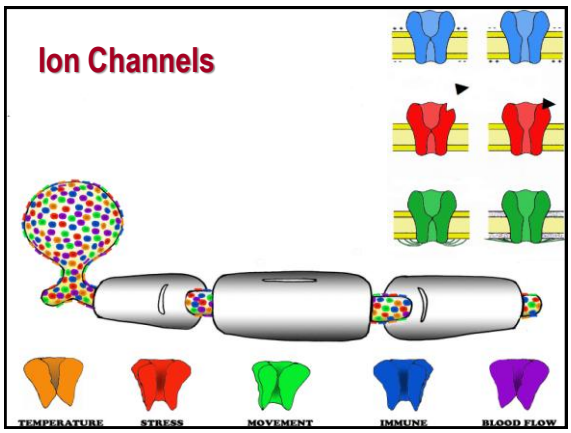
## Remember these?

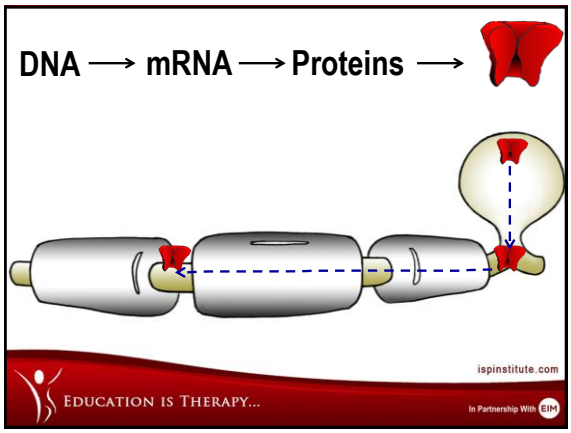



## Ion Channels

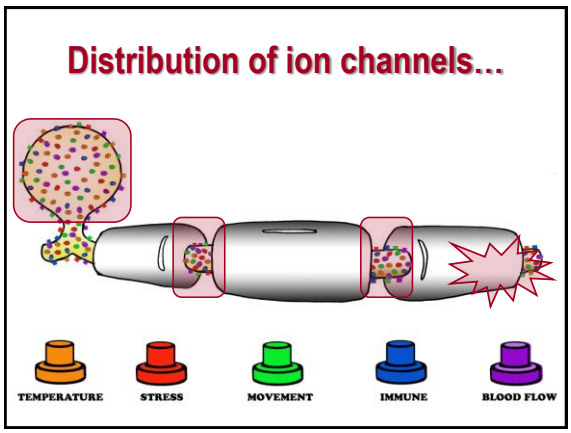


## Ion Channels

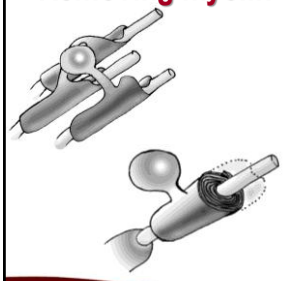








## Removing myelin



- Mechanical
- Immune
- Chemical

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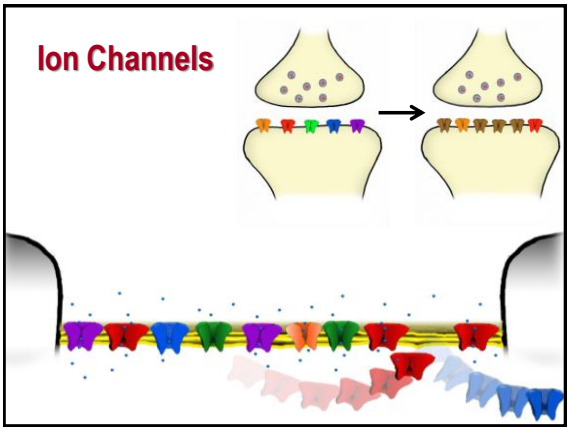
## Ion Channels



## Recap...CRPS (peripheral neuropathic)

- Genetics/family – ion channel expression
- Stress/Anxiety
  - High level of initial pain – adrenaline ion channels
  - Fracture, surgery, sprain – adrenaline ion channels
- Temperature sensitization – ion channels
- Female/male - ? Hormonal/ion channels
- Immobilization – movement channels
- Extreme sensitization – nerve up-regulation
- Spreading pain – connected nervous system

More to come...

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## Key pathophysiological changes

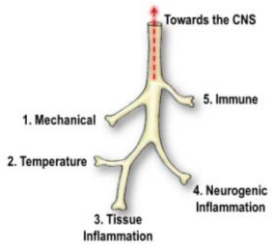
- **Three major pathophysiological pathways:**
  1. **Aberrant inflammatory mechanisms**
  2. **Vasomotor dysfunction**
  3. **Maladaptive neuroplasticity.**



## 1. Aberrant inflammatory mechanisms

## Ever had inflammatory soup?

## Tissue Inflammation




**TISSUE INFLAMMATION**

When tissues get injured, there is an inflammatory "soup" that ensues with release of various chemicals in/around the tissues by the damaged cell membranes: bradykinin, prostaglandin, serotonin, leukotrienes, etc. (Drummond 2010) The immune cells also release macrophages, cytokines and histamine via mast cells (Dickerson, Undem et al. 1998). This is sterile inflammation, normal and designed for protection and healing. With these processes there is stiffness > pain.

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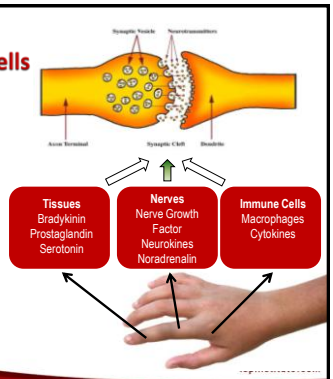
## Inflammation:
### More inflammatory cells

- Minor tissue trauma increase cytokine signaling in the injured tissue
- **Cytokines** and nerve growth factor **(NGF)** wake up nociceptors and increase nerve sensitivity

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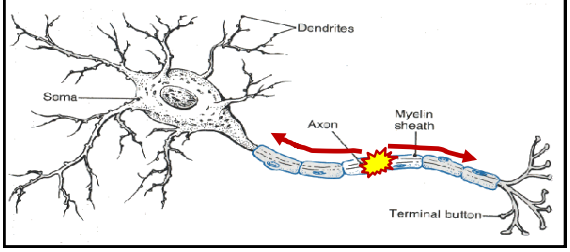
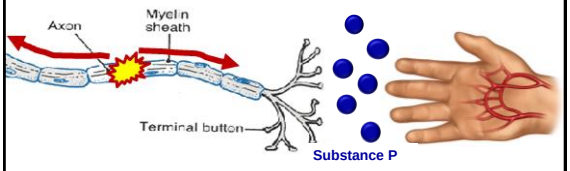
## Inflammation: Nerves go both ways

- Activation of cutaneous nociceptors can induce retrograde depolarization of small-diameter primary afferents (axon reflex), causing the release of neuropeptides such as substance P and calcitonin-gene-related peptide (CGRP).

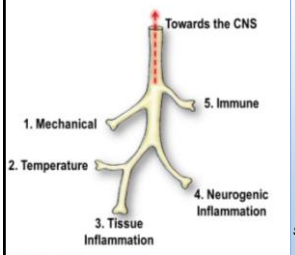


## Inflammation: Nerves go both ways

- Neuropeptides promote vasodilation and protein extravasation (cells leaking from capillaries) in the tissue:
  - Neurogenic inflammation
  - Redness, warm and swelling




## Neurogenic Inflammation




**NEUROGENIC INFLAMMATION**

Via antidromic impulses (retrograde depolarization), nerves fire "backward" and facilitate **increased release of substance-P**, noradrenaline, neurokines, calcitonin-gene-related peptides, nerve growth factor, etc. Substance P is vasoactive and contributes to mast cell degranulation, which release histamine. This in turn signals macrophages and enzymes to facilitate "mop up" of the chemicals and part of the healing process (Nordin, Nystrom et al. 1984).These chemical releases infuse the "soup" with more inflammatory cells, and activate nociceptors, thus increasing CNS barrage. *Neurogenic inflammation is characterized by persistent swelling and inflammation and can be driven by thoughts.*

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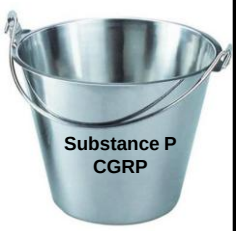
## Neurogenic Inflammation increases

- Serum concentrations of CGRP and substance P – **higher in patients with CRPS** than in healthy control individuals.
- Elevated CGRP release is probably responsible for the augmented **flare** response in patients with CRPS

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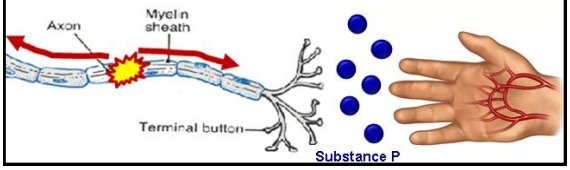
## Inflammation: Blood vessels open up (more later)

- **Mechanism for neurogenic inflammation**
  - Substance P produces greater extravasation in both the affected and the unaffected limbs of patients with CRPS than in control individuals.




## Inflammatory soup develops

- Facilitated cutaneous neuropeptide signaling contributes directly to the enhanced extravasation, limb edema, and increased **cytokine** expression that are present in CRPS.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## Inflammation increases nerve sensitivity

- **Cytokine** changes are associated with the extent of mechanical hyperalgesia
- **Mechanical hyperalgesia**
  - Hallmark of central sensitization
  - Excitability of neurons in the spinal cord is increased
- **Inflammatory cytokines:**
  - Acts locally in the limb
  - Sensitization of secondary nociceptive neurons in the spinal cord or by glial–neuronal interaction.

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## Glia in the spinal cord?

- Or neuroglia (Greek for "glue"), classically = cells that provide metabolic & structural support, but also:
  - Establish & maintain synapses
  - Regeneration and plasticity
  - Myelin formation/repair
  - Immune function
- Outnumber neurons >10 to 1

D Fields (2004) April – Sci Amer

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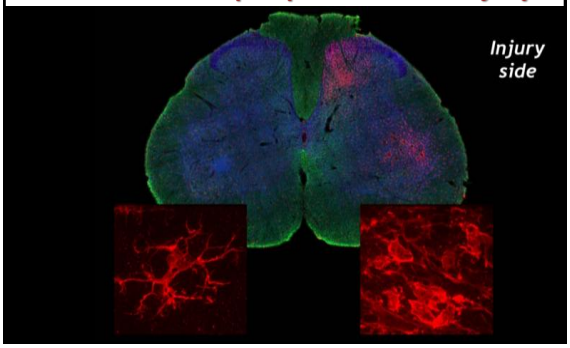
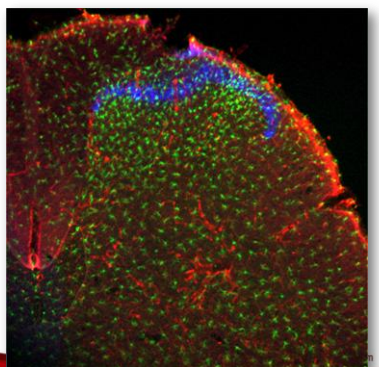
## Response of microglia in the spinal cord after peripheral nerve injury




A cascade of immune changes start to occur…



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Injury to a peripheral nerve and electrical stimulation of C-fibers each cause an increase in the permeability of the blood-spinal cord barrier and blood-brain barrier

Beggs S, Liu XJ, Kwan C, Salter MW. Peripheral nerve injury and TRPV1-expressing primary afferent C-fibers cause opening of the blood-brain barrier. *Mol Pain*. 2010;6:74.



## Summary

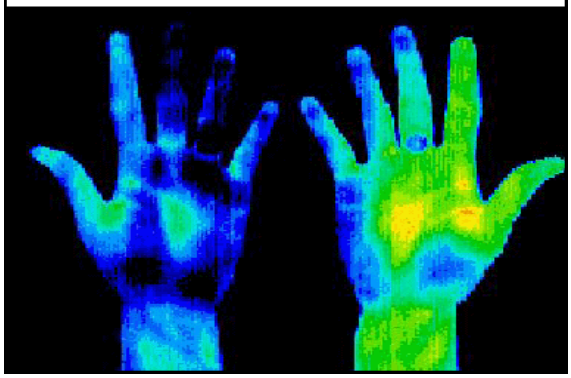
- The changes in the spinal cord however, also track up to the brain and affect the blood-brain barrier
- Changes in blood-brain-barrier leads to changes in the body maps in the brain
  - Smudging occurs
  - With smudging, the brain has a hard time recognizing "self" from "non-self"
- This activates the immune system, especially cytokine (Costigan, Moss et al. 2009)



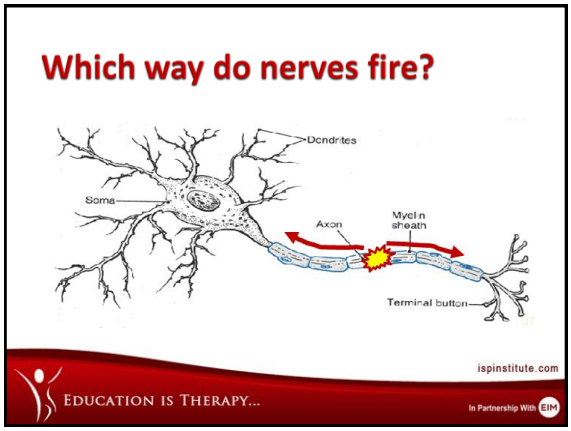
## Summary

- With increased cytokine activity (Devor 2006)
  - Ion channel upregulation with increased widespread sensitization
  - Persistent swelling
  - Investigation and clinical awareness of old injuries "waking up"
- With the increased "smudging of the maps"
  - Nervous system is upregulated (allodynia)
  - Altered temperature
  - Neglect

## 2. Vasomotor dysfunction

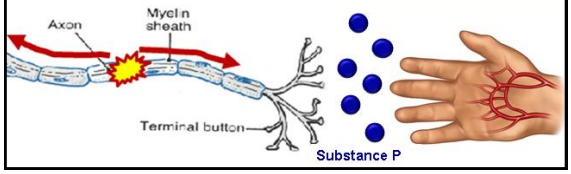


## Which way do nerves fire?



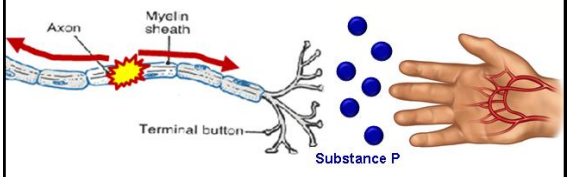

## Antidromic impulses

- Substance P release
- Capillaries open
- Swelling
- Warmth



## Antidromic impulses

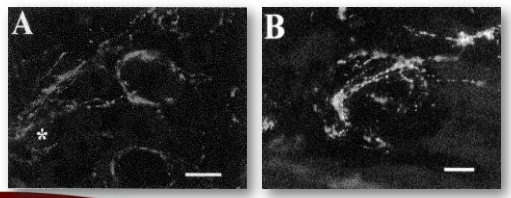
- Substance P
  - Mast cells degranulation
  - Histamine
- Increased Enzyme activity




## Sympathetic Sprouting and basket weaving

Causes and consequences of sympathetic basket formation in dorsal root ganglia

Matt S. Ramer, Stephen W.N. Thompson, Stephen B. McMahon*




Pain Supplement 6 (1999) S111–S120 .com

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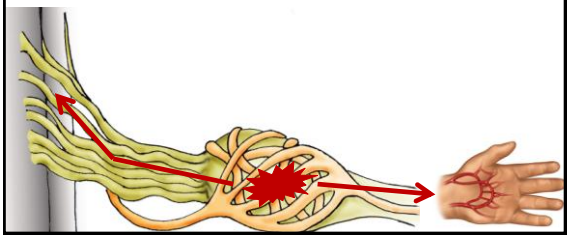
## SNS is efferent & contribute to pain by:

- Dorsal root ganglion – non-myelinated
- Sympathetic axonal sprouting and weaving around DRG, releasing more adrenaline onto it
  - 70% of the adrenal receptors in the body live in the DRG
- Nerve fires….both ways



## Vasomotor

- Common in CRPS
- Affected limb:
  - Usually warmer than the healthy limb early on
  - Colder than the healthy limb later
  - Temperature shift - activity in vasoconstrictor neurons
  - Three distinct patterns of temperature change:
    1. Warm type
    2. Intermediate type
    3. Cold type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## Vasomotor

- **Warm type**
  - Affected limb **warmer** and skin perfusion values were higher than the contralateral limb (CPRS for a mean of 4 months).
  - **Norepinephrine** concentrations from the venous effluent above the painful area are lower in the affected limb than in the contralateral one.

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## Vasomotor

- **Intermediate type**
  - Temperature and perfusion **either warmer or colder**, depending on the amount of sympathetic activity (mean disease duration of 15 months).
- **Cold type**
  - Temperature and perfusion in the affected limb consistently **lower** than those in the contralateral limb (mean of 28 months).
  - **Norepinephrine** concentrations lower on the affected side.

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## Vasomotor

- Inhibition of cutaneous sympathetic vasoconstrictor neurons
- Thermoregulatory impairment probably caused by functional changes in the **spinal cord, brainstem, or brain** that are triggered by the initial trauma.

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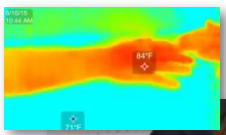

Moseley GL, Olthof N, Venema A, et al. Psychologically induced cooling of a specific body part caused by the illusory ownership of an artificial counterpart. *Proc Natl Acad Sci U S A.* Sep 2 2008;105(35):13169-13173.
Walsh LD, Moseley GL, Taylor JL, Gandevia SC. Proprioceptive signals contribute to the sense of body ownership. *The Journal of physiology.* Jun 15 2011;589(Pt 12):3009-3021

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## Vasomotor

- There are suggestions that cutaneous sympathetic vasoconstrictor activity returns to normal as CRPS persists, even though the limb becomes cold and bluish.

## Vasomotor

- Central disturbances – acute
- Neurovascular transmission – chronic

- About 20% of patients with CRPS have the cold type from the start. These patients not only differ in skin temperature but also in sensory symptoms and history.



## Vasomotor

- The **sympathetic nervous system**, in addition to its effect on peripheral circulation in CRPS, might also contribute to pain.
- Nociceptors develop **catecholamine sensitivity**, probably as a result of decreased activity of cutaneous sympathetic vasoconstrictor neurons.
- **Norepinephrine** released by the sympathetic nerve fibers activate or sensitize the altered afferent neurons.

## Easy huh?

- Maybe you can start seeing why it is **COMPLEX** regional pain syndrome…

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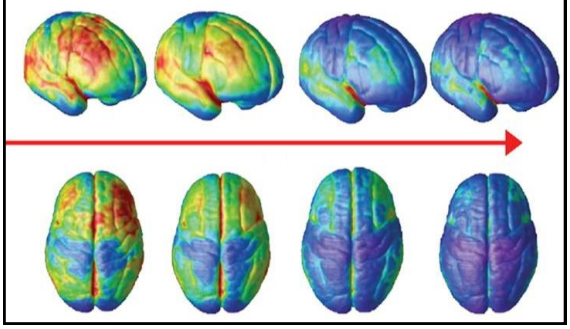
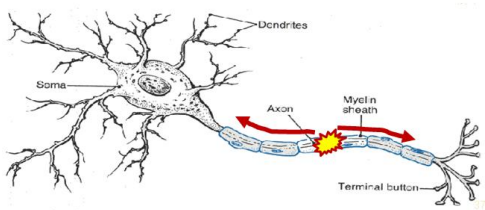
## 3. Maladaptive neuroplasticity



## Which way do nerves fire?

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## In CRPS there is a structural and functional neuroplastic change that occurs…

1. Driven by the brain
2. To protect/survive

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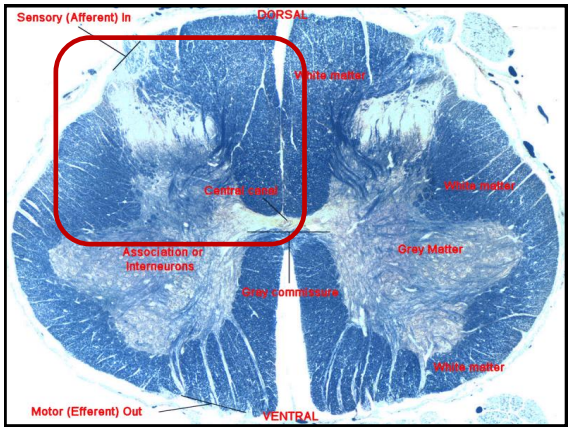


## If you can answer this, you're well on your way:

- What is 1 + 1?

5

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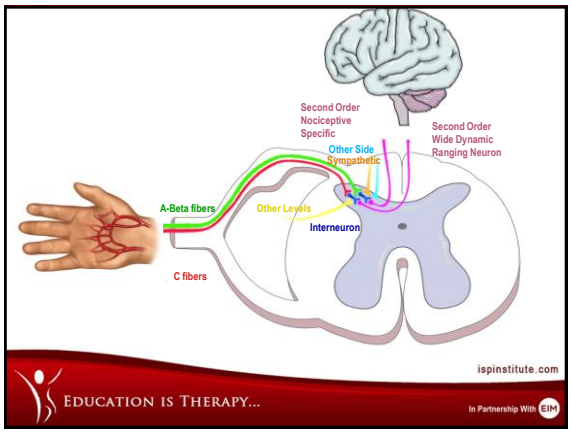
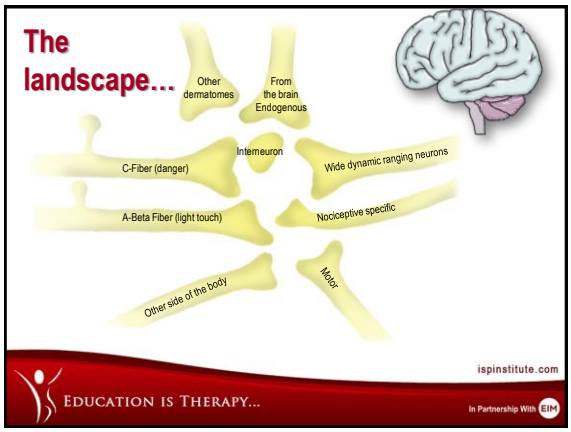
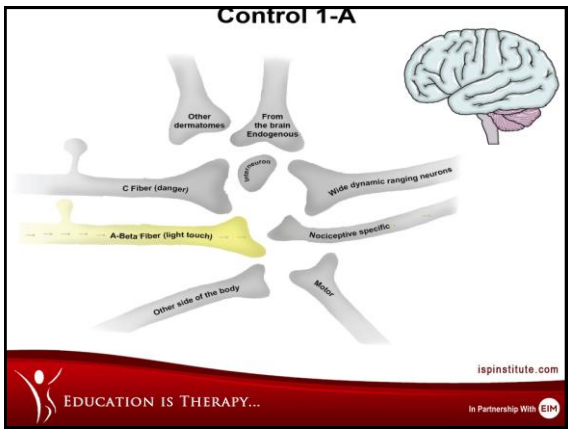
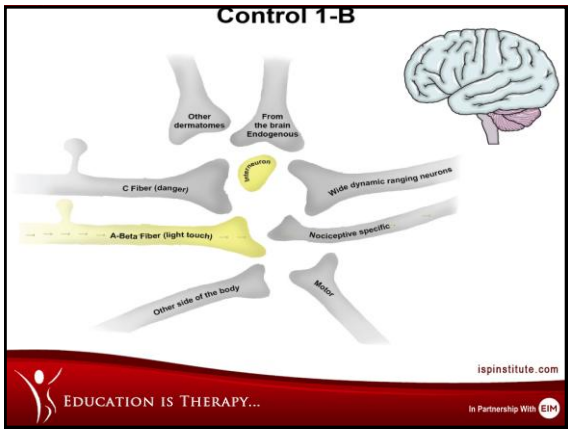
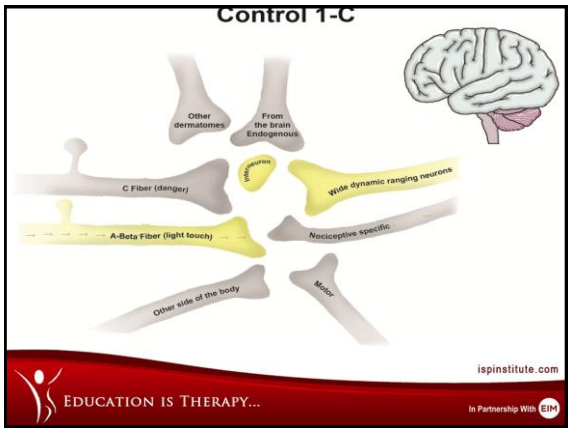
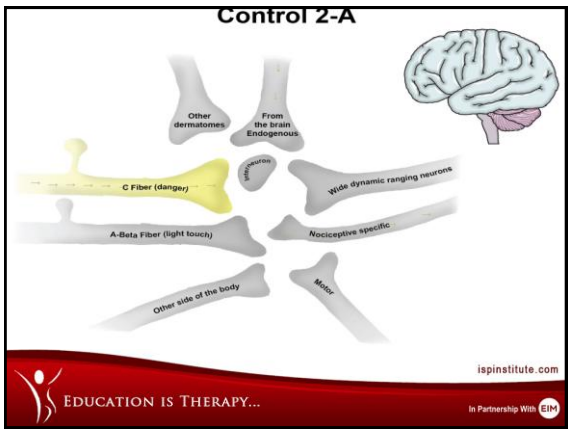


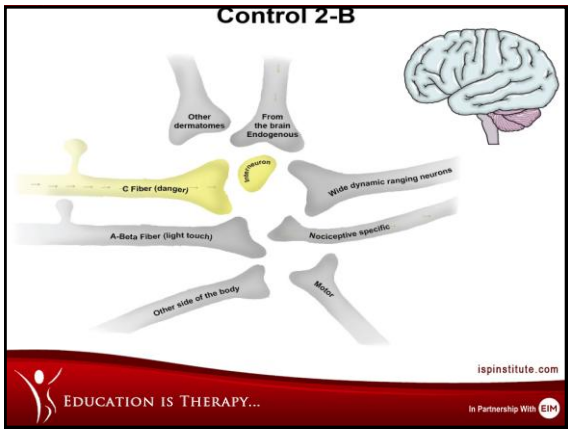



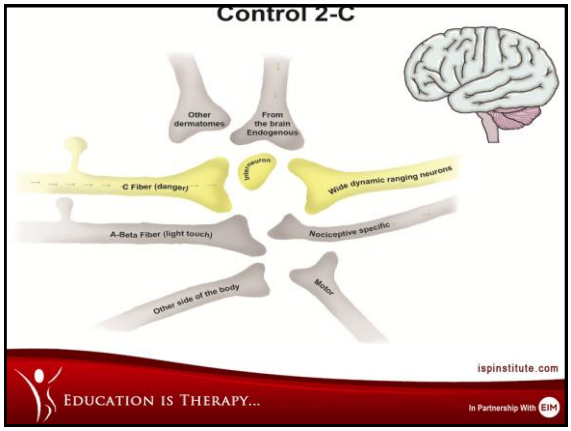



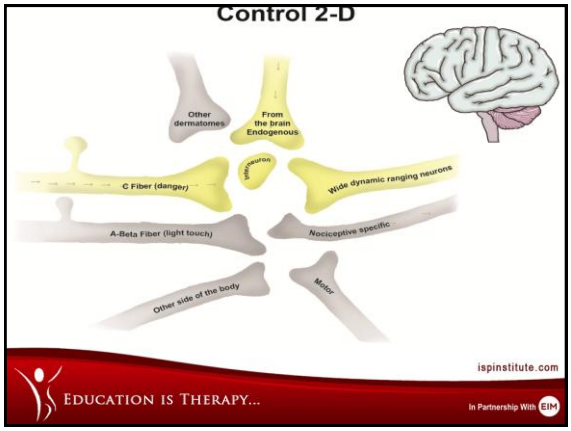


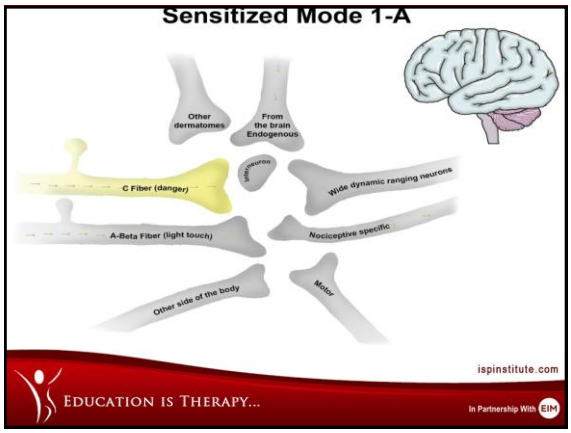



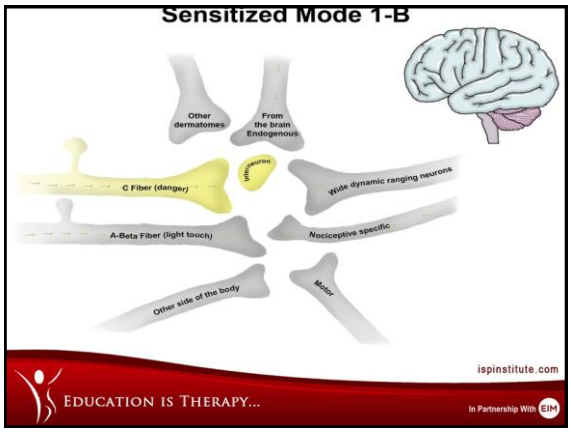



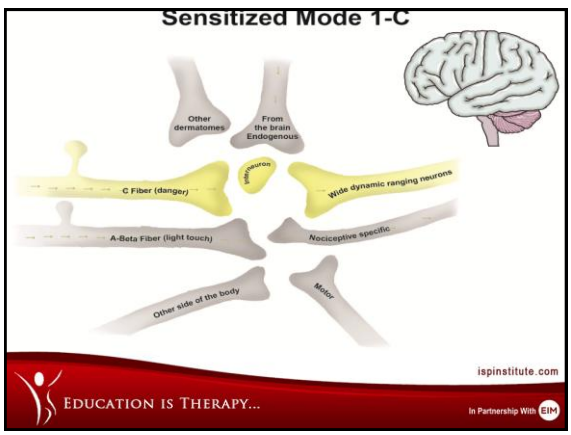


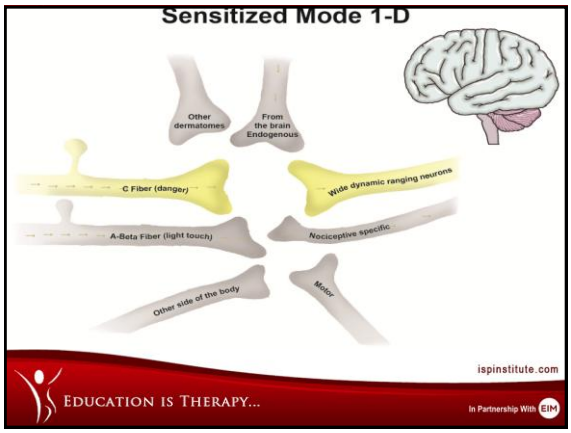



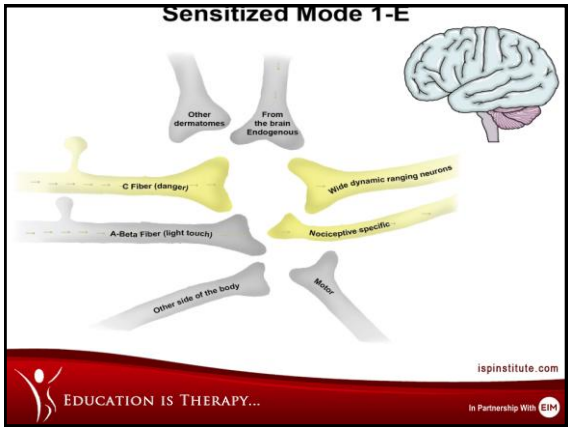



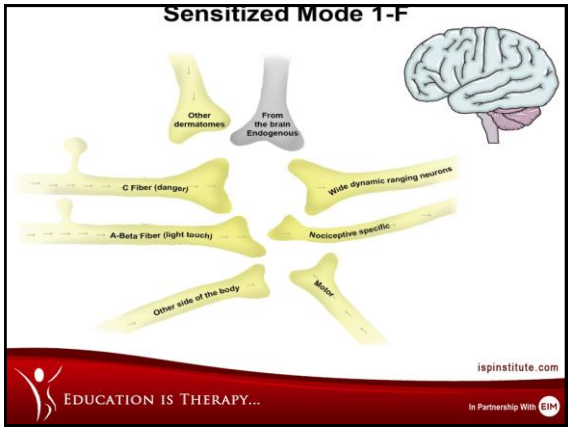


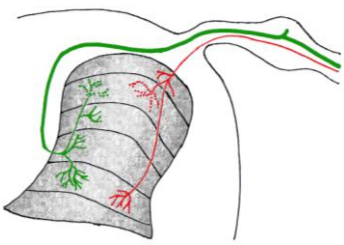


## Allodynia

A-beta grows in
C-fibers die back



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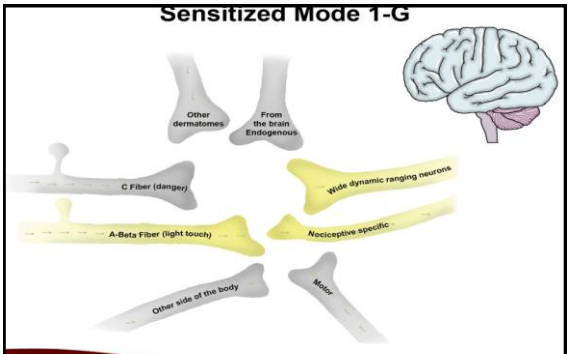
## Sensitized Mode 1-G

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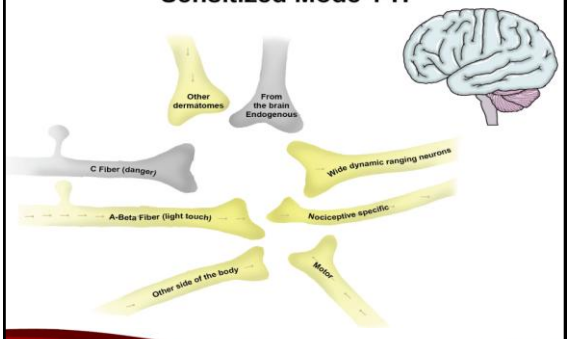
## Sensitized Mode 1-H

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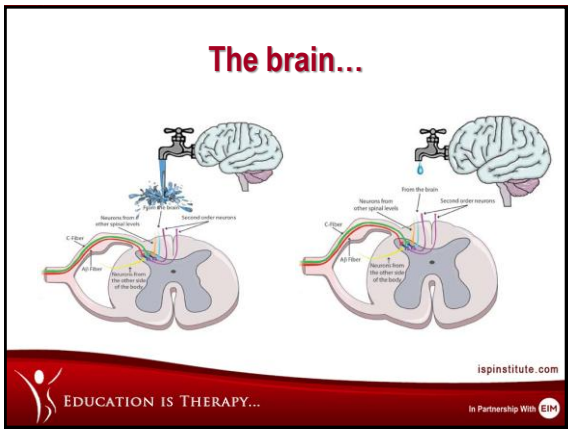


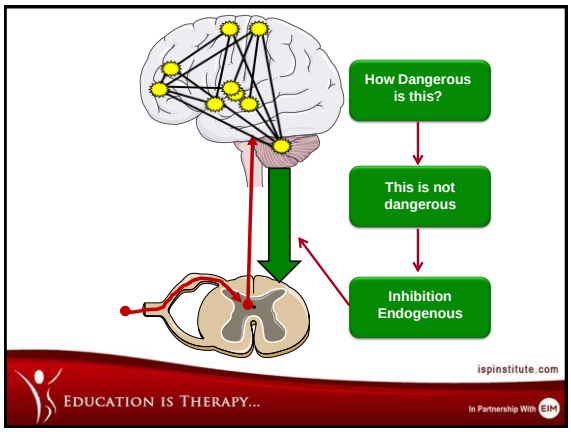


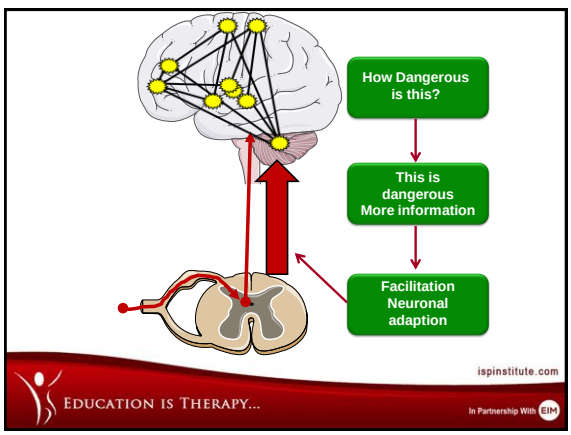

## End-Result

| Process | Consequence |
|---|---|
| • Death of the inhibitory neurons | • Decreased gating from the periphery |
| • C-fibers pull back; A-fibers grow in | • Allodynia |
| • Up-regulation of second-order neurons | • Increased firing towards the brain |
| • Inappropriate synapsing – other levels | • Spreading pain |
| • Inappropriate synapsing – other fibers | • Sympathetic, immune, motor contributions |
| • Inappropriate synapsing – other side | • Bilateral "mirror" pains |
| • Decreased endogenous mechanisms | • Allodynia and Hyperalgesia |

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## 3. Neuroplasticity

- The CNS undergoes **functional** and **structural changes** in people with persistent pain

↓

Central Sensitization

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## Neuroplasticity

- Sensitized spinal nociceptive neurons become:
  - More responsive to peripheral input
  - Might even fire in the absence of such input
- Central sensitization can cause chronic pain, hyperalgesia, and allodynia, as well as the spreading hyperalgesic priming

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## Neuroplasticity

- In some patients a **transient insult** can lead to chronic pain
- A transient insult triggers long lasting changes in primary afferent nociceptors that prime them to become hyper-responsive to future mild insults that would normally not evoke pain in the unprimed state.

**NEXT INJURY!!!!!**

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## Neuroplasticity

- **Impaired motor function**
  - **Common** after most injuries but generally resolves
  - In CRPS susceptible patients develop **marked movement disorders.**
  - **Dystonia** - most prevalent movement disorder in CRPS
  - Characterized in the arm by persistent flexion postures of the fingers and wrist

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## Neuroplasticity

- The risk of **dystonia** spreading to additional limbs in patients with CRPS increases with the number of limbs that are already dystonic.
- This accelerated disease course is a typical characteristic of **maladaptive neuronal plasticity.**

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## Want the BAD NEWS?

- CRPS is a brain disorder
- We have only really covered the periphery to this point
- We have not even covered the brain yet
- This is where the MAJOR changes occur

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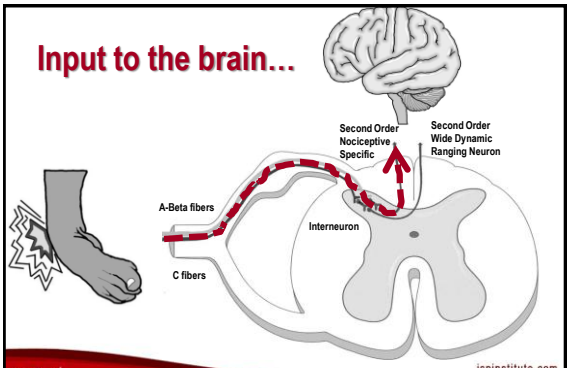
## Input to the brain…

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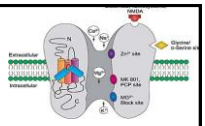
## Neuroplasticity



- Activation and up-regulation of **glutamate** receptors, which enhance signal transmission in the nociceptive circuitry from the spinal cord to the cerebral cortex
  - Glutamate – excitatory neurotransmitter
  - 70% of all brain synapses are glutamate synapses

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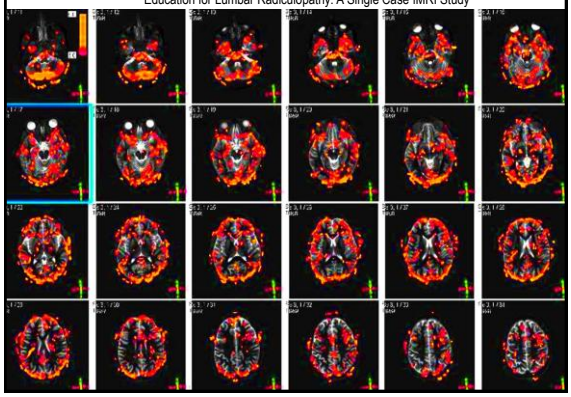
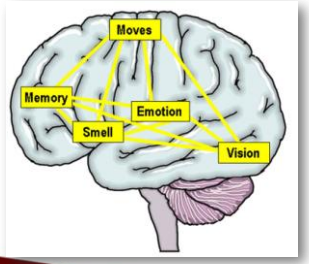
Louw A, Butler DS, Diener I, Puentedura E and Peoples, R; 2015 Preoperative Neuroscience Education for Lumbar Radiculopathy: A Single Case fMRI Study



## The Brain's Processing (Blobolobby 101)...Grandma

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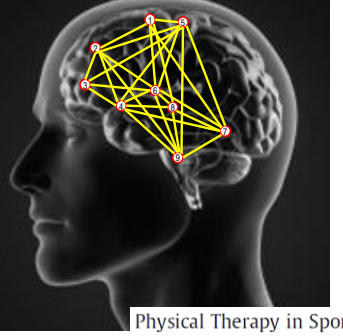
## A TYPICAL PAIN NEUROTAG

1. PREMOTOR/ MOTOR CORTEX
   *organize and prepare movements*
2. CINGULATE CORTEX
   *concentration, focusing*
3. PREFRONTAL CORTEX
   *problem solving, memory*
4. AMYGDALA
   *fear, fear conditioning, addiction*
5. SENSORY CORTEX
   *sensory discrimination*
6. HYPOTHALAMUS/ THALAMUS
   *stress responses, autonomic regulation, motivation*
7. CEREBELLUM
   *movement and cognition*
8. HIPPOCAMPUS
   *memory, spacial recognition, fear conditioning*
9. SPINAL CORD
   *gating from the periphery*

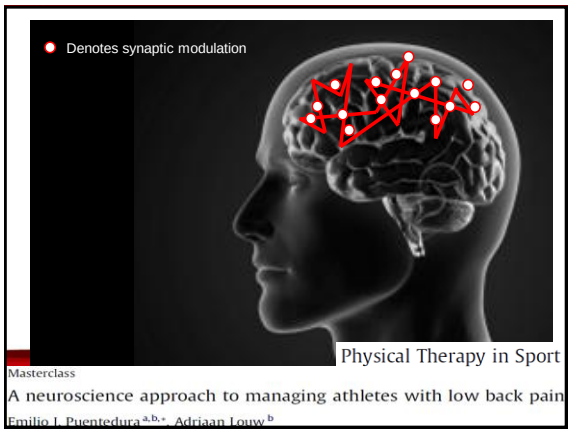


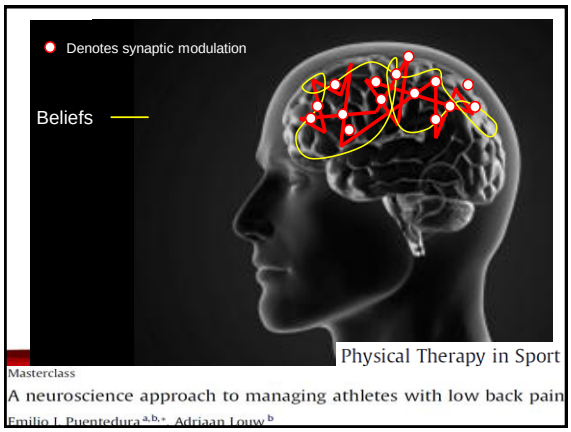
Physical Therapy in Sport

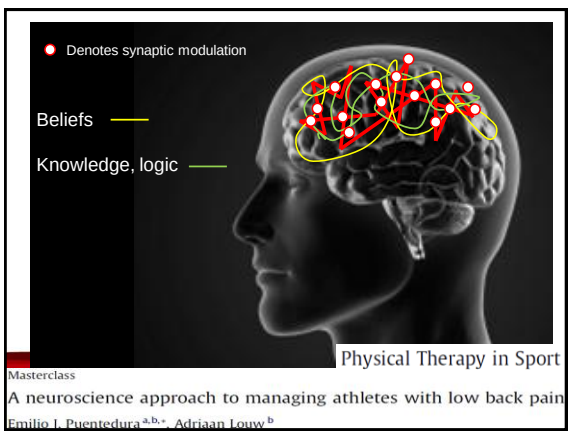
Masterclass

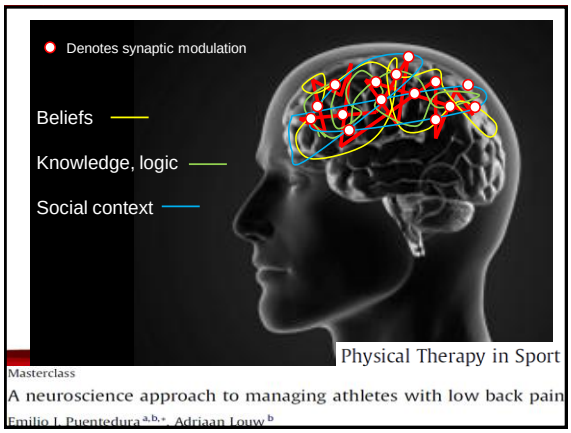
A neuroscience approach to managing athletes with low back pain

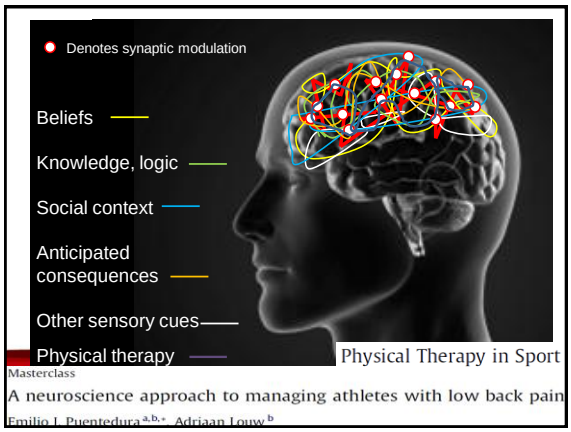
Emilio J. Puentedura [a,b,*], Adriaan Louw [b]

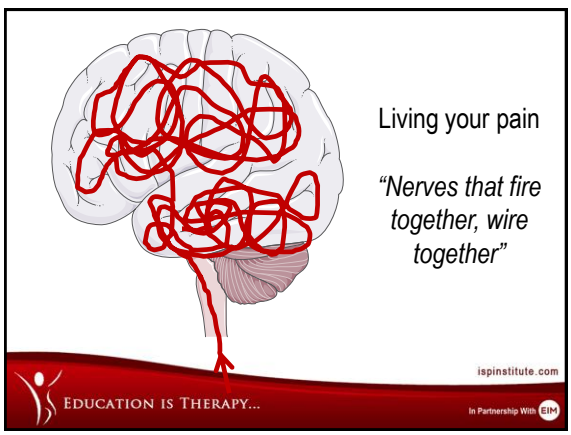


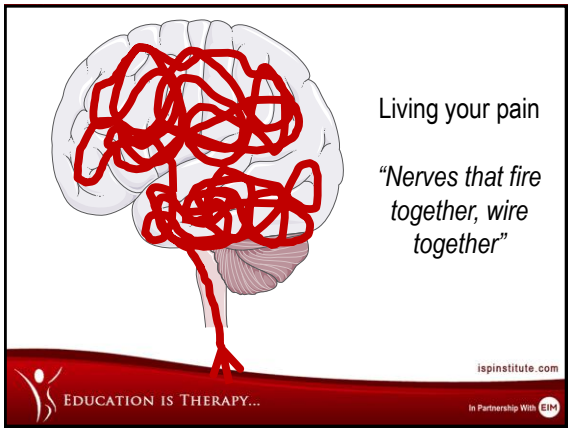








## Neuroplasticity

- The CNS undergoes functional and structural changes in people with persistent pain
- Leads to central sensitization
- Changes occur in structures involved in the **emotional** aspects of pain
  - Amygdala
  - Anterior cingulate
  - Prefrontal cortex

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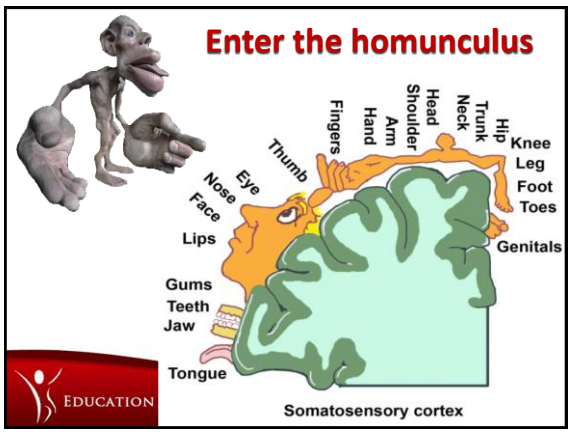
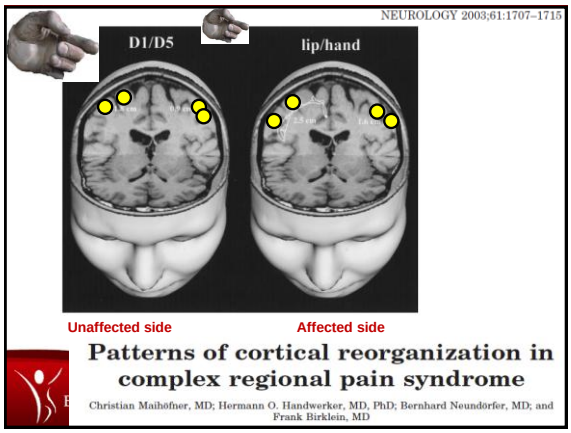
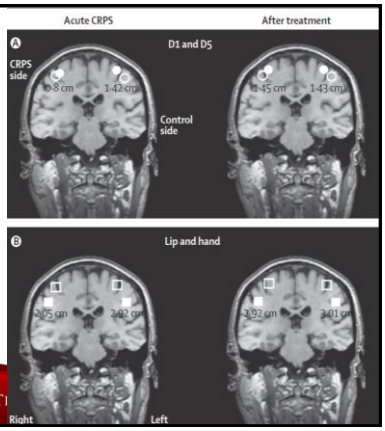





## fMRI

Substantial **reorganization of the somatotopic map within the primary somatosensory cortex (S1)** contralateral to the affected limb in patients with CRPS.

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## Neuroplasticity

- **Cortical reorganization might explain:**
  - The spatial distribution of sensory disturbances in a **glove-like** or **stocking-like** pattern, the occurrence of tactile induced referred sensations
  - The perception that the limb is bigger than it really is, and the presence of hemi-sensory deficits.

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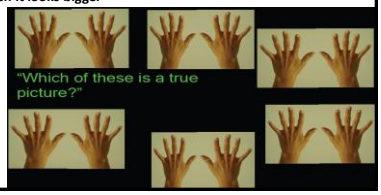
## Neuroplasticity

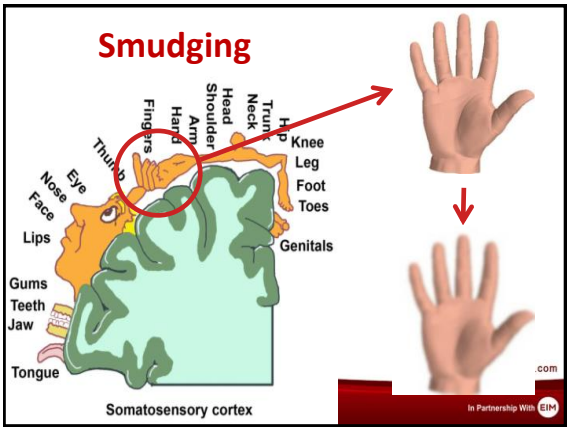
- People with longstanding CRPS tend to perceive their affected limb to be larger than it really is.
  - CRPS patient believes the hand feels 107% bigger
    - **Hurts more when it looks bigger**
    - **Does not move different**
    - **More swelling when it looks bigger**

**Visual distortion of a limb modulates the pain and swelling evoked by movement**

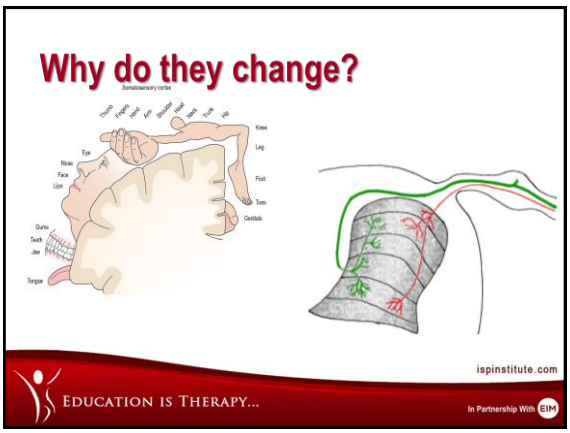
G. Lorimer Moseley[1,2], Timothy J. Parsons[1] and Charles Spence[3]



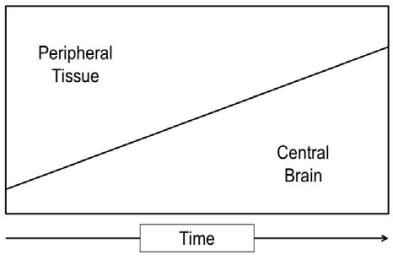

## Smudging




## Why do they change?



## Sensitivity

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## Central Sensitization Inventory

**Central Sensitivity Inventory**

Scale range is 0-100
Answers and scoring method

- Never = 0
- Rarely = 1
- Sometimes = 2
- Often = 3
- Always = 4

1. I feel refreshed when I wake in the morning
2. My muscles feel stiff and achy
3. I have anxiety attacks
4. I grind or clench my teeth
5. I have problems with diarrhea and or constipation
6. I need help in performing my ADL's
7. I am sensitive to bright lights
8. I get tired very easily with physical activity
9. I feel pain all over my body
10. I have headaches
11. I feel discomfort in my bladder
12. I do not sleep well
13. I have difficulty concentrating
14. I have skin problems (dry, itchy, rashes)
15. Stress makes my physical symptoms worse
16. I feel sad or depressed
17. I have low energy
18. I have tension in my muscles
19. I have pain in my jaw
20. Certain smells make me dizzy/nauseated
21. I have to urinate frequently
22. My legs feel uncomfortable and restless at night
23. I have difficulty remembering things
24. I suffered trauma as a child
25. I have pain in my pelvic area

*Mayer et al (2912) Pain Pract – NIH Pub Access*

## This is not mine

- Distortions of the mental image of their limb
- Missing components or alterations in shape, posture, and temperature of the whole limb or of discrete parts of the limb.

Pain 133 (2007) 111–119

Body perception disturbance: A contribution to pain in complex regional pain syndrome (CRPS)

Jennifer S. Lewis [a,b,*], Paula Kersten [b], Candida S. McCabe [a,c], Kathryn M. McPherson [d], David R. Blake [a,c]

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## Neuroplasticity

- Aware of their altered feelings towards the limb
- Although they believe that the limb is theirs, they feel as though it is not
- Neglect-like disturbances reported in CRPS are a result of:
  - Avoid provocation of pain
  - Altered representation of aspects of the limb



## Neuroplasticity

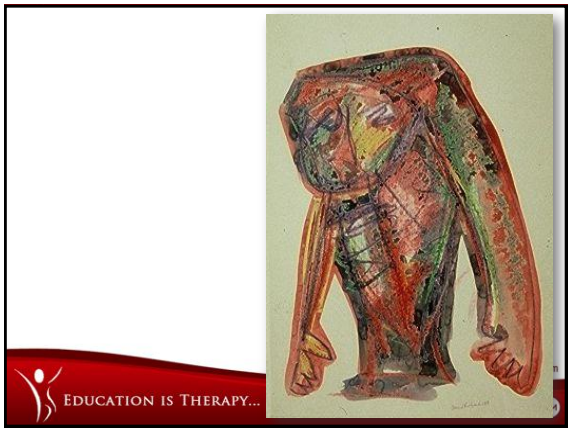
- Feelings of **hostility** or **disgust** towards the affected limb
- Feel as though it is a **separate entity**
- Foreign body that they would **like to have amputated**

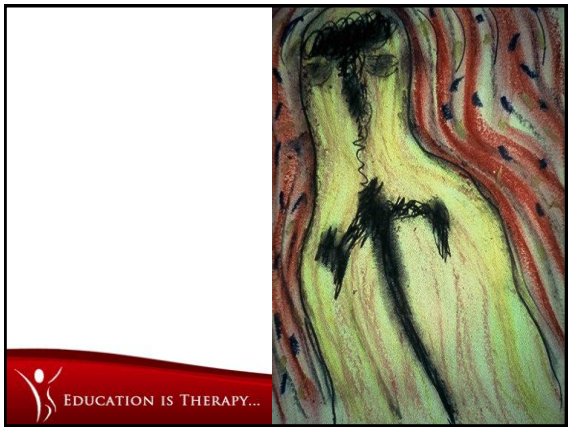
Pain 133 (2007) 111–119

Body perception disturbance: A contribution to pain in complex regional pain syndrome (CRPS)

Jennifer S. Lewis [a,b,*], Paula Kersten [b], Candida S. McCabe [a,c], Kathryn M. McPherson [d], David R. Blake [a,c]






## Recent E-mail

- From: OT; To: Adriaan@ispinstitute.com
- Subject: question about CRPS patient
- Date: Wed, 24 Jul 2013 13:57:25 -0500

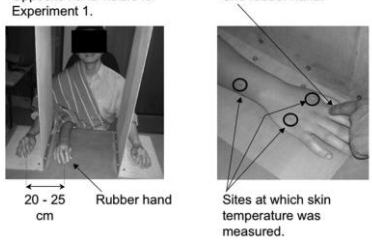
I have a question about a young gal I am seeing now with CRPS. She is 18 years old. When she first came to see me she had no motion in her right arm and pain 9/10. Within 3 months she had full motion, pain at 1/10 and using her arm for all ADL's. A month ago she hurt her wrist picking up her cat and is now almost back to square one with pain 9/10, and no motion distal to the elbow. She was catastrophizing initially, but that has stopped now. She is using her right arm for gross motor activities, so not total neglect. Today she tells me that she does not feel like she has a right arm, and when she looks in the mirror she sees two left arms. She knows she is looking at her right arm, but says it looks like her left arm. She also said that when she is touching her right arm it feels like she is touching her left arm.

PNAS | September 2, 2008 | vol. 105 | no. 35 | 13173

**Neuroplasticity made easy…**

A Participant's hands placed behind screens. Opposite hand visible for Experiment 1.

B Synchronous manual brushing of real hand and rubber hand.







**Psychologically induced cooling of a specific body part caused by the illusory ownership of an artificial counterpart**

G. Lorimer Moseley*†, Nick Olthof‡, Annemeike Venema‡, Sanneke Don‡, Marijke Wijers‡, Alberto Gallace§¶, and Charles Spence§

## Neuroplasticity

- Swelling and pain evoked by movement of the CRPS-affected limb is more severe if patients view a magnified image of the limb; if it looked bigger, it hurt more and became more swollen.

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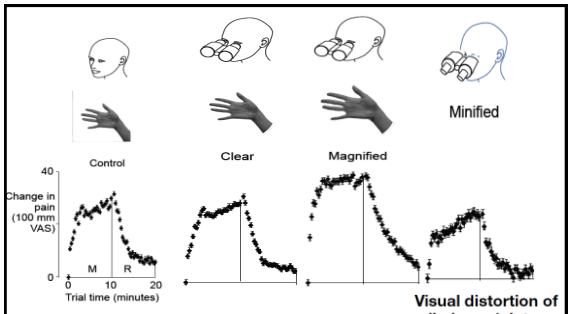
Current Biology Vol 18 No 22 R1048

**Visual distortion of a limb modulates the pain and swelling evoked by movement**

G. Lorimer Moseley[1,2], Timothy J. Parsons[1] and Charles Spence[2]

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Current Biology Vol 18 No 22 R1048

Visual distortion of a limb modulates the pain and swelling evoked by movement

G. Lorimer Moseley[1,2], Timothy J. Parsons[1] and Charles Spence[2]

## Neuroplasticity

- The perceptual disturbances in CRPS similar to disturbances associated with unilateral neglect after stroke.
  - Patients can perceive touch on the affected limb if they watch the mirror image of the unaffected limb being touched.
  - **Acerra & Moseley 2005 Neurology 65; 751-753**

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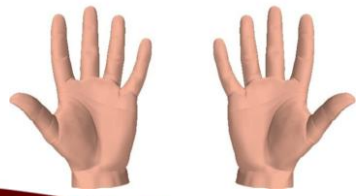
## Neuroplasticity

- Patients perform poorly on tasks in which they are required to judge the laterality of a pictured limb.



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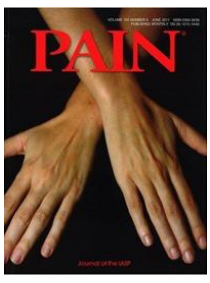
## Neuroplasticity

- Recent work has suggested that cold-type CRPS is associated with a cold side of space—i.e., crossing the arms so that the healthy hand is on the affected side of the midline **reduces the temperature of the healthy hand**




Gallace A, Torta DM, Moseley GL, Iannetti GD. The analgesic effect of crossing the arms. *Pain.* Jun 2011;152(6):1418-1423.

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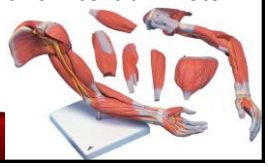
## Neuroplasticity

- Cortical changes also affect the primary **motor cortex** in patients with CRPS.
- Decreased inhibitory mechanisms and **increased excitability in the contralateral primary motor cortex** in patients with CRPS.
- Widespread impairment of central motor processing in CRPS.



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## Summary

1. High levels of acute pain, immobilization and increased inflammation seems to predict CRPS development.
2. With the above factors, there is likely an immediate **up-regulation** of the peripheral and central nervous system. Thus, nerves become *extra sensitive*.
3. Nerves fire both ways.
4. Nerves firing down to the extremity produce increased **inflammatory and immune cells**, which causes swelling, heat and sensitivity. These changes likely influence the sensory and motor maps in the brain. The brain sees the hand/foot altered and becomes concerned about limited hand/foot use.

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## Summary

5. The peripheral nervous system **fires into the CNS**, causing long-lasting neuroplastic events culminating in central sensitization. This additionally confuses the brain, leading to changes in the maps related to the specific body part.
6. There is an **immune response** in the blood-spinal cord barrier which alters the brain's view of the hand/foot.
7. **Thoughts are nerve impulses** and the impulses drive both orthodromic and antidromic (retrograde) depolarization, leading to persistent inflammation and central nervous system plasticity changes.

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## Summary

8. The **whole brain** processes all the danger and thus, busy with pain, facilitates changes in various output systems, including motor control, immune and endocrine system.
9. **Maps of the body parts are altered** in the brain (CNS, visual, peripheral and immune system altering the blood-brain barrier), resulting in the extremity looking different, usually larger, and problems discerning left and right.
10. With increased confusion, the brain bring in its most potent defender: **PAIN.**



## Treatment…

- **Of the 3 major pathophysiological pathways it seems neuroplasticity may be a BIG PART:**
  1. **Aberrant inflammatory mechanisms**
  2. **Vasomotor dysfunction**
  3. **Maladaptive neuroplasticity**



## Testing a Sensitive Nervous System

Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. Manual therapy. Apr 2010;15(2):135-141.

Overview of the clinical examination of patients with suspected central sensitization.[a]

| Clinical tests |
|---|
| 1. Assessment of pressure pain thresholds at sites remote from the symptomatic site |
| 2. Assessment of sensitivity to touch during manual palpation at sites remote from the symptomatic site |
| 3. Assessment of sensitivity to vibration at sites remote from the symptomatic site |
| 4. Assessment of sensitivity to heat at sites remote from the symptomatic site |
| 5. Assessment of sensitivity to cold at sites remote from the symptomatic site |
| 6. Assessment of pressure pain thresholds during and following exercise |
| 7. Assessment of joint end feel |
| 8. Brachial plexus provocation test |

## Altered Body Maps

**How to identify smudging**

- *f*MRI, PET, TMS, MEG in a research lab
- In a clinical setting:
  - Draw a person [modified]
  - Complex sensory testing
  - Laterality or mental rotation or left-right discrimination (motor imagery & its components)
  - TPD


"OK, Mrs. Dunn. We'll slide you in there, scan your brain, and see if we can find out why you've been having these spells of claustrophobia."

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## Two Point Discrimination

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## Pressure Pain Thresholds

Castro-Sanchez, A. M., M. E. Aguilar-Ferrandiz, et al. (2014). "Short-term Effects of a Manual Therapy Protocol on Pain, Physical Function, Quality of Sleep, Depressive Symptoms, and Pressure Sensitivity in Women and Men With Fibromyalgia Syndrome: A Randomized Controlled Trial." The Clinical journal of pain 30(7): 589-597.
Fernandez-de-Las-Penas, C., P. Madeleine, et al. (2009). "Generalized neck-shoulder hyperalgesia in chronic tension-type headache and unilateral migraine assessed by pressure pain sensitivity topographical maps of the trapezius muscle." Cephalalgia.
Fuentes, J., S. Armijo-Olivo, et al. (2014). "Enhanced therapeutic alliance modulates pain intensity and muscle pain sensitivity in patients with chronic low back pain: an experimental controlled study." Physical therapy 94(4): 477-489.
Meeus, M., J. Nijs, et al. (2012). "Role of psychological aspects in both chronic pain and in daily functioning in chronic fatigue syndrome: a prospective longitudinal study." Clinical rheumatology 31(6): 921-929.
O'Sullivan, P., R. Waller, et al. (2014 chronic non-specific low back pain: A subgroup investigation." Manual therapy 19(4): 311-318

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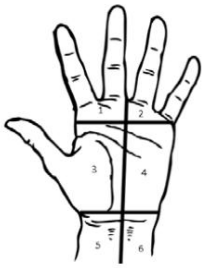
## Localization testing

- Where was I touched?
  *(and where was it that I hurt?)*
- Stimulus from clinician then identification from patient:
  - Grid identification
  - Tactile localization (measure error distance)
- Impaired tactile acuity relates to impaired motor control

Luomajoki & Moseley (2011), Wand et al (2010, 2011)



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## Left/Right Discrimination/ Laterality

Image from noi


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## Laterality impairment

- Site-specific disruption in left right judgments have been reported with:
  - Amputees
  - CRPS
  - Chronic back pain
  - CTS
  - Knee OA
  - Arm and hand pain
  - Dystonia
  - Post stroke
  - Expectation of pain
  - Radiculopathy

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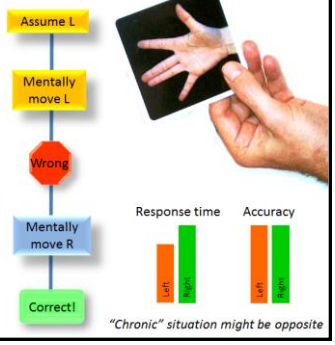
## What's *normal*?

- Accuracy of >80%
- 1.6 sec +/- 0.5 for necks and backs
- 2 sec +/- 0.5 for hands and feet




## Treatment

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## Treatment: Fundamental Flaw

As long as the brain does not understand the pain and does not even know what left and right are, there is no incentive to reduce it's most potent protector:

**PAIN**

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## Classic Rehabilitation

Missing Piece

- Do part of movement but no painful part
- Do part of movement with painful part
- Do more
- Increase number
- Increase strength
- Add equipment

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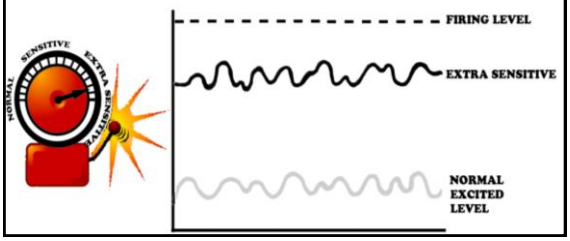
## Treatment: Fundamental Flaw

As long as pain and sensitivity is so high, the extremity does not want to be touched, moved or used




## In Central Sensitization...

- **Phase 1:**
  - Decrease sensitivity and pain
- **Phase 2:**
  - Move towards function, movement, goals, etc.

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## Proposed Treatment

- Therapeutic Neuroscience Education
- Graded Motor Imagery
- Sensory Discrimination
- Regular Therapy
  - Sensory integration
  - ROM
  - Function
  - Etc.

So the brain understands
↓
Restoring the extremity/body part back in the brain
↓
Function/ROM

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## Our recommendation

Sequence Matters:

1. Therapeutic Neuroscience Education
2. Left/Right Discrimination
3. Motor Imagery
4. Sensory Discrimination and Graphesthesia
5. Mirror Therapy

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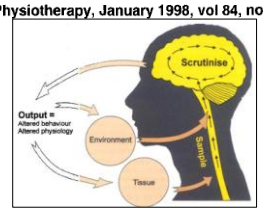
## Origins of Neuroscience Education

**Pain, the Tissues and the Nervous System: A conceptual model**

*Louis Gifford*

Physiotherapy, January 1998, vol 84, no 1



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## TNE: Content

- Neurophysiology of pain
- No reference to anatomical or patho-anatomical models
- No discussion of emotional or behavioral aspects to pain
- Nociception and nociceptive pathways
- Neurons
- Synapses
- Action potential
- Spinal inhibition and facilitation
- Peripheral sensitization
- Central sensitization
- Plasticity of the nervous system

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## Efficacy Neuroscience Education

**Conclusions:** For chronic MSK pain disorders, there is compelling evidence that an educational strategy addressing neurophysiology and neurobiology of pain can have a positive effect on pain, disability, catastrophization, and physical performance.

UNIVERSITEIT STELLENBOSCH UNIVERSITY

Louw A, Diener I, Butler DS, Puentedura EJ. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Archives of physical medicine and rehabilitation.* Dec 2011;92(12):2041-2056.

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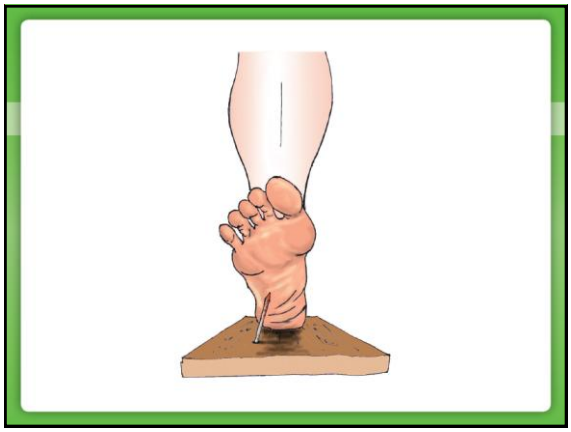
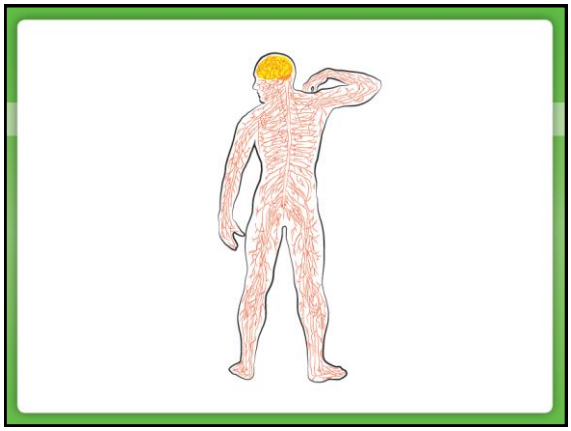
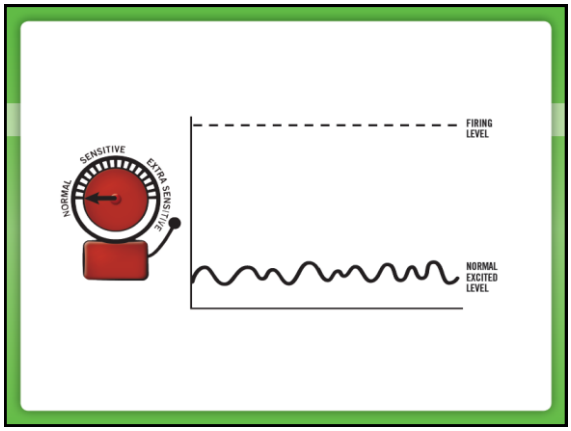
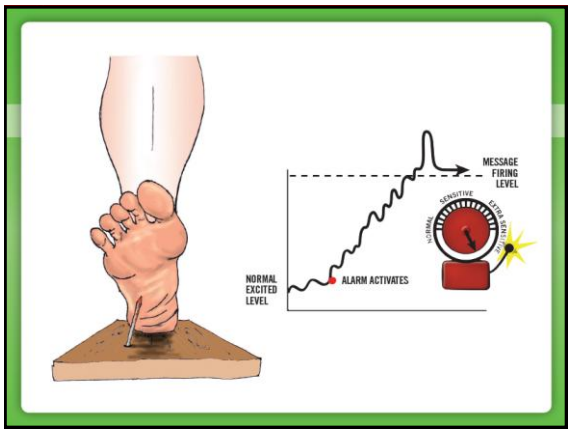
## Section 2. Sensitive Nerves

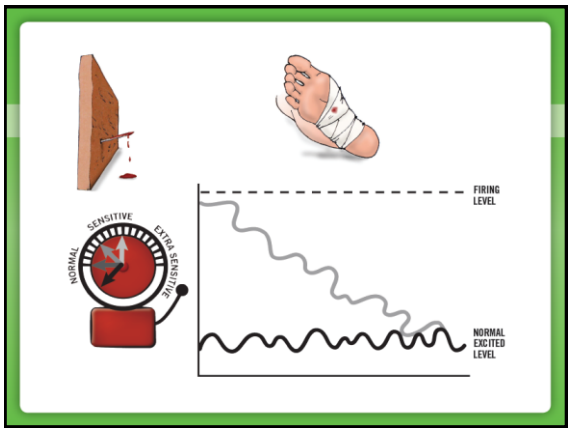
- Peripheral neuropathic pain
- Peripheral nerve sensitization
- Central sensitization
- Hyperalgesia
- Allodynia

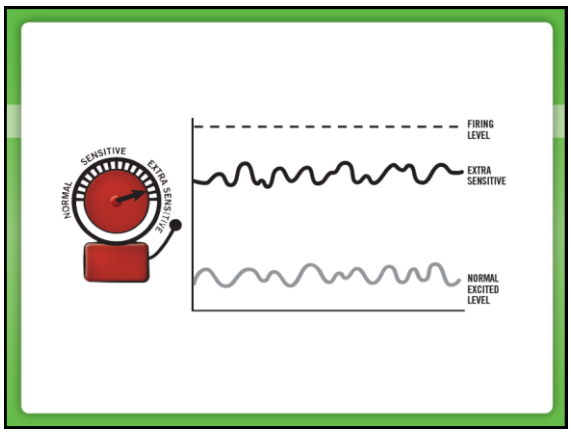


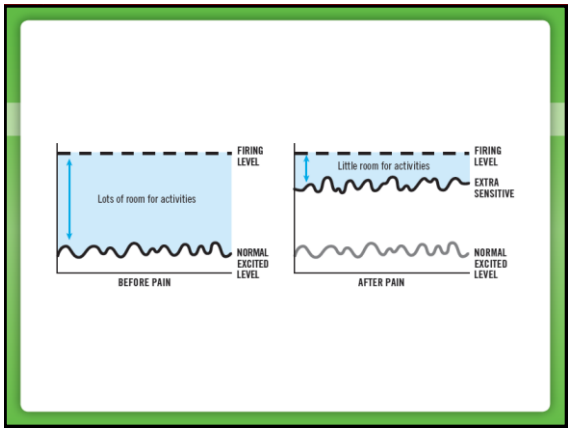


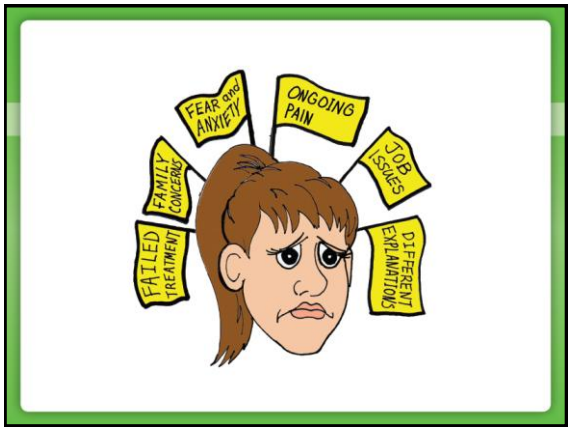




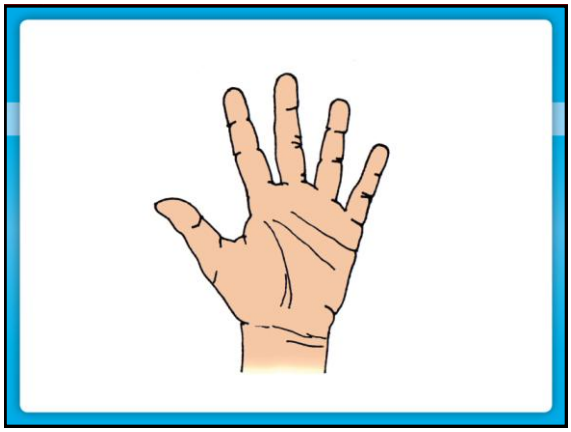



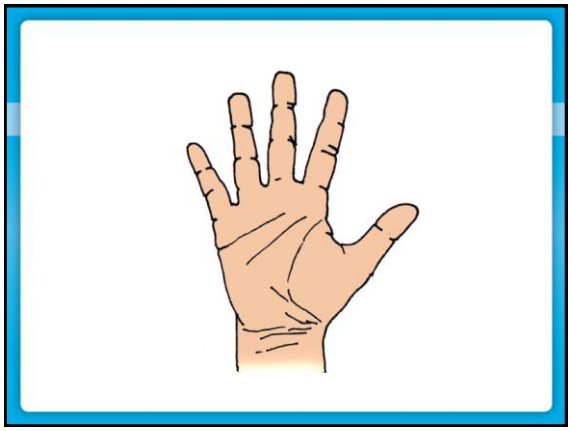


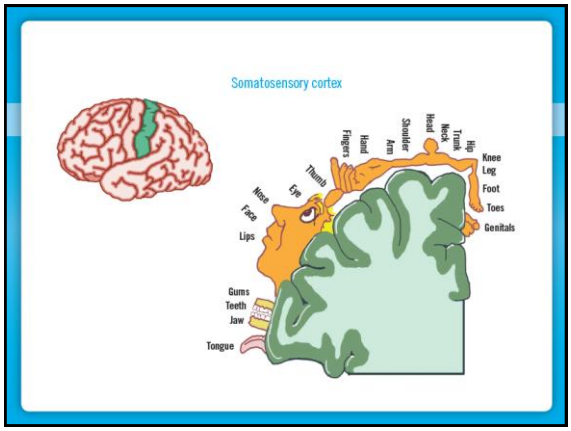



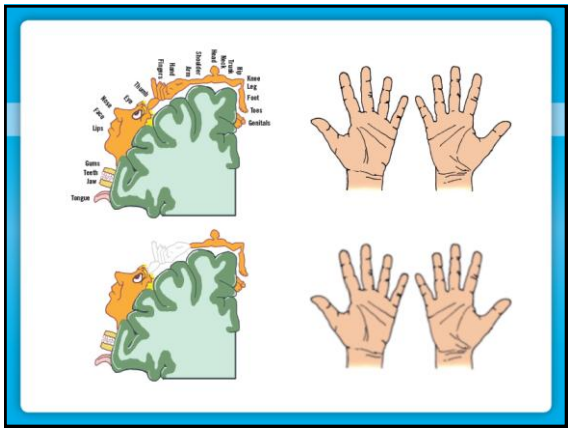

## Section 12. The Brain's Body Maps

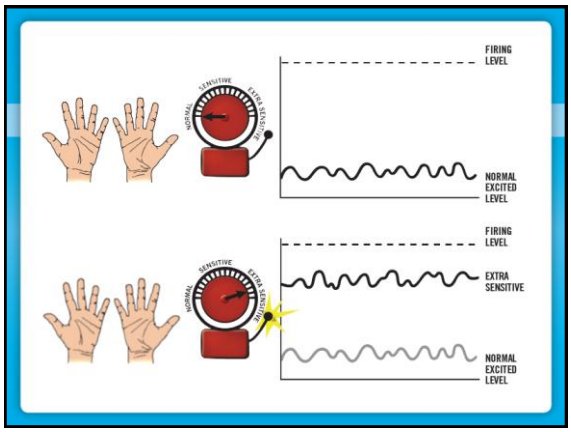
- Neuroplasticity
- Homunculus
- Sensory cortex
- Phantom limb pain
- Complex regional pain syndrome
- Use it or lose it
- Spreading pain
- Neglect
- Laterality
- Smudging
- Graded motor imagery

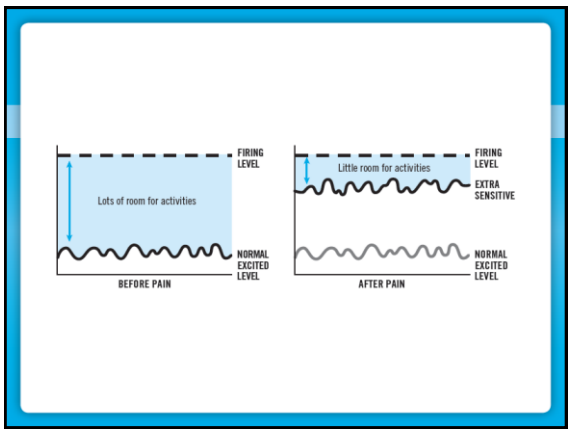


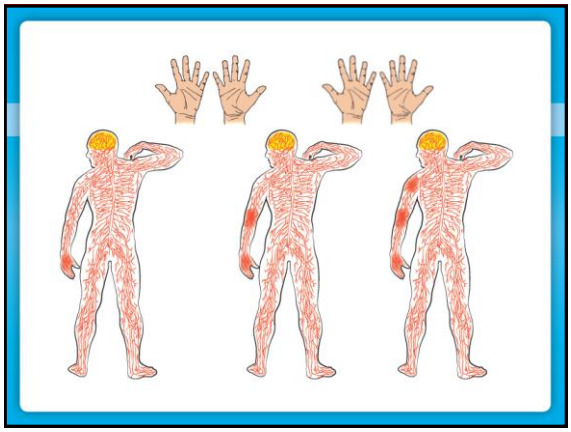


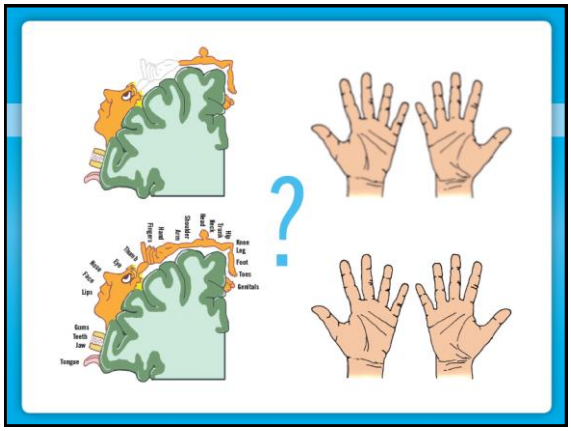


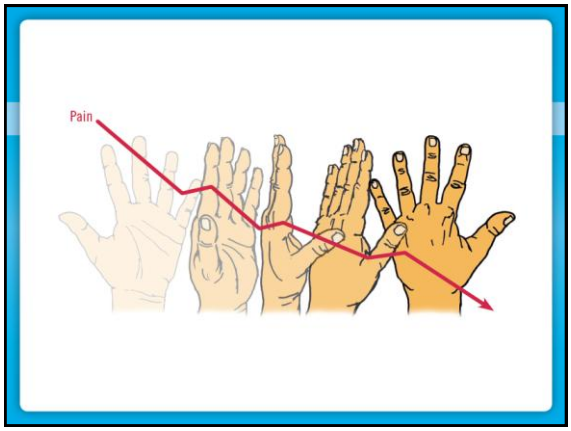


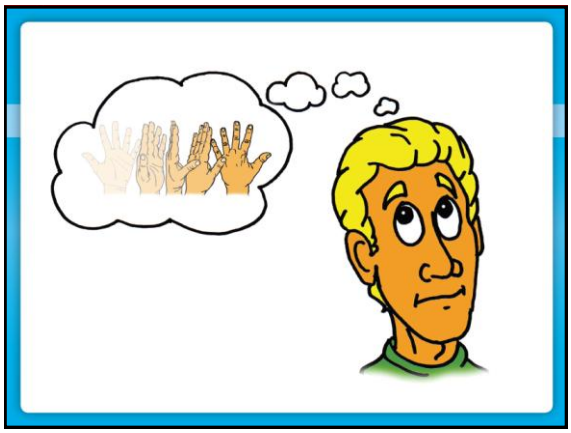



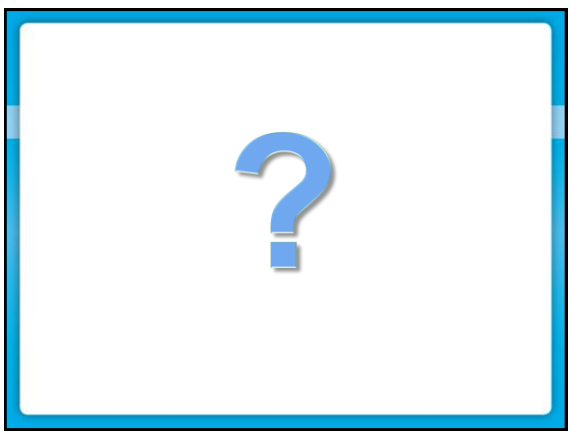









## Phase 2: Laterality

**Left/right discrimination is the accuracy and speed of identifying whether a picture or body part is a right or left**

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## Phase 2: Laterality

- Cards – Internet Images






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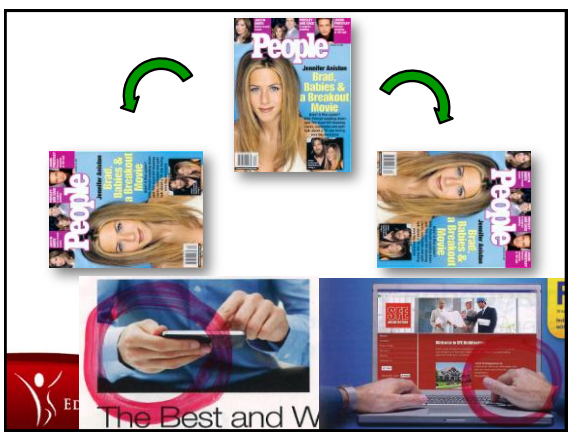

## Phase 2: Laterality

- Magazines
- Make flash cards
  - Internet images
  - Take photos
- Make a PowerPoint
- noigroup.com
  - Flashcards
  - Online
  - Smartphone publications


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## Phase 2: Laterality

- Emotions
- L/R should be continued
- Injury, pain and immobilization

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## Phase 2: Laterality

- GOAL:
  - Under 3 seconds
  - > 80% accurate (? 90)
- Hands versus feet
- Dyslexia
- 10-20% no shift; move on

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## Recent e-mail from a PT

- Hello Again!
  First, I'd like to say thank you for the guidance you've given me already; second I'd like to say that I've had success in treating my patient with CRPS, but now I am not sure how to proceed.
- Here's the quick story, we started with looking at pictures of feet--playing games with the pictures (matching, sorting, etc.)... and on day 5 the patient woke up with almost total resolution of his pain. He was down to a 2/10. The pain remained low, and by the next day he had 0/10 pain. Yippee!

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## Phase 3: Imagery

- Why do you yawn, when you see someone else yawning?
- Easiest way to start urinating?

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## Evidence

European Journal of Pain 13 (2009) 339–353

Contents lists available at ScienceDirect

European Journal of Pain

journal homepage: www.EuropeanJournalPain.com

Review

Does evidence support physiotherapy management of adult Complex Regional Pain Syndrome Type One? A systematic review

Anne E. Daly [a,b,*], Andrea E. Bialocerkowski [b]

**Narrative synthesis of the results, based on effect size, found there was good to very good quality level II evidence that graded motor imagery is effective in reducing pain in adults with CRPS-1, irrespective of the outcome measure used.**

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## Phase 3: Imagery

- Imagine extremity (see it visually)
  - Static
  - Dynamic
  - Doing tasks
- Giving the brain map exercise without moving the extra sensitive extremity

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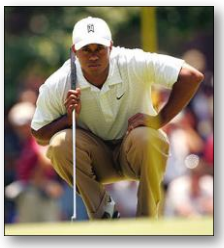
## Phase 3: Imagery

- Been used for years in sports
- Very important potential role in acute/severe pain



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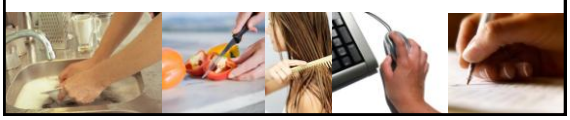
## Phase 3: Imagery - Example

- Ask patient for top 10 tasks needed to be performed with painful extremity
- Find 10 such activities/images on the Internet
- Draw card; imagine static hand in that position
- Imagine moving hand to similar position
- Imagine performing the task
- Repeat; repeat; repeat



## Phase 3: Imagery - Example

- CRPS Foot



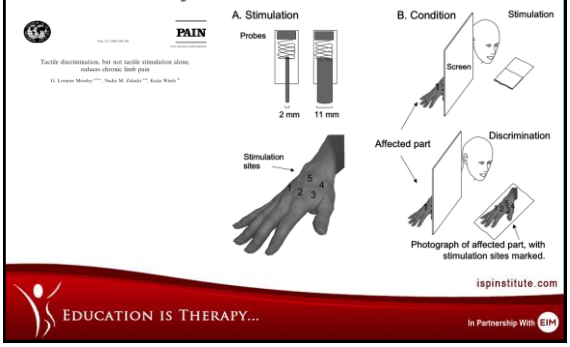
## Phase 4: Fundamental flaw



## 4. Sensory Discrimination

- Why discrimination and not integration?

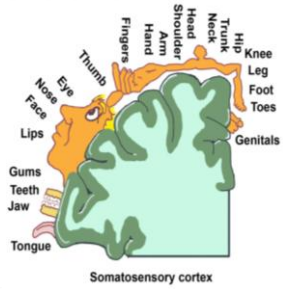
## 4. Sensory Discrimination




## 4. Sensory Discrimination

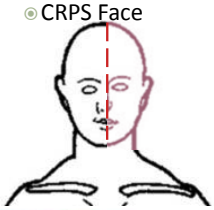

## 4. But: It's too sensitive...

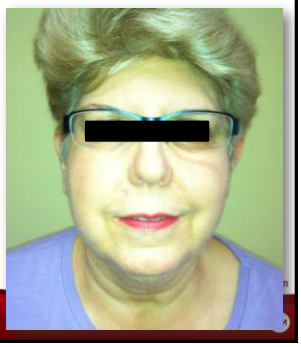
- If you know your neighbors, you can find your house



## 4. Sensory Discrimination

- Patient Example
- CRPS Face





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## 4. Sensory Discrimination

- Patient Example – Hypersensitive feet s/p MVC

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## 4. Graphesthesia training

| | | | | | |
|---|---|---|---|---|---|
| **Easier**: examples with few similarities in shape, # strokes or direction changes | | | | | |
| O | I | X | W | Z | E |
| + | - | □ | / | ○ | ✳ |
| 0 | 1 | 2 | 4 | 7 | |
| **Moderate**: examples with some similarities in shape, # strokes or direction changes: e.g. E vs. F, M vs. N | | | | | |
| E | F | M | N | □ | △ |
| > | ✓ | 8 | 5 | 3 | 2 |
| **More challenging**: some examples with similar shape, # strokes or direction changes: e.g. J vs. L vs. 7 or 6 vs. 9 (similar shapes in different orientation), rectangle vs. square vs. diamond (similar shapes but different sizes or rotated) | | | | | |
| J | L | U | V | X | K |
| P | D | Q | R | B | E |
| 6 | 9 | 7 | ▯ | □ | ◇ |

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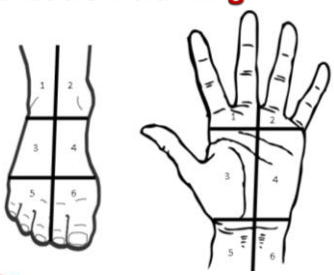
## 4. Localization training



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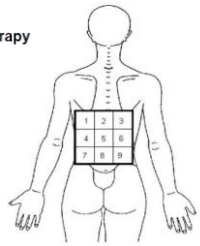
New Zealand Journal of Physiotherapy

PHYSIOTHERAPY NEW ZEALAND
Kōmiri Aotearoa

St Ambrose University



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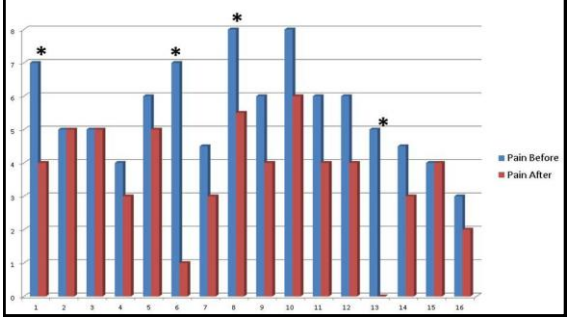

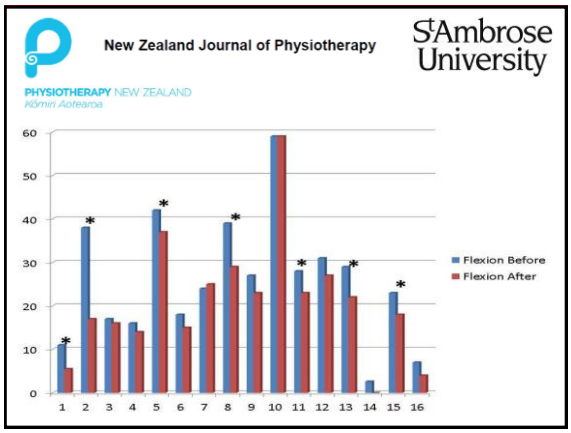


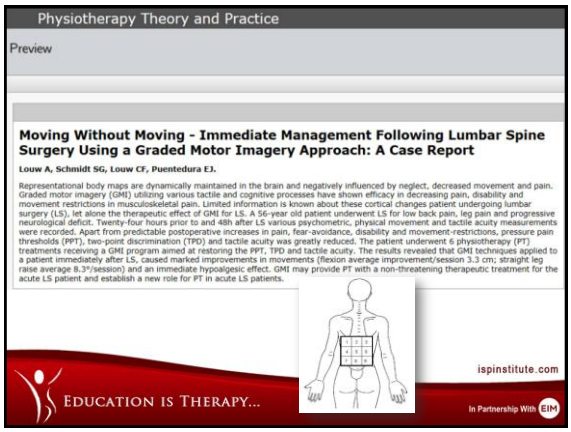


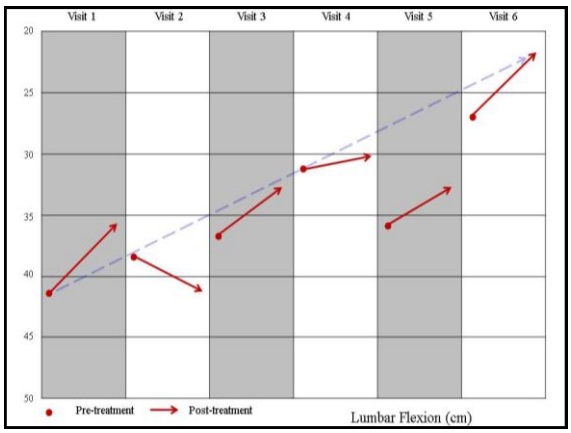

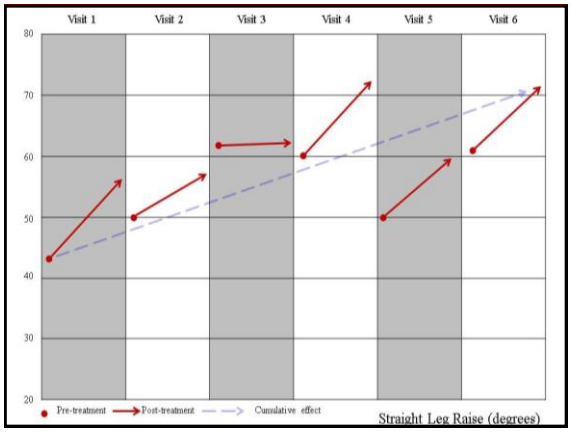


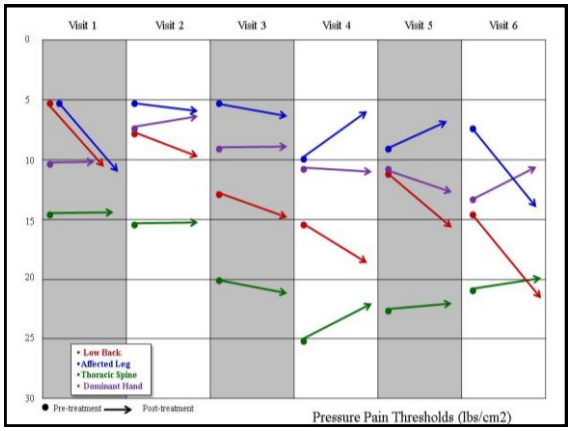


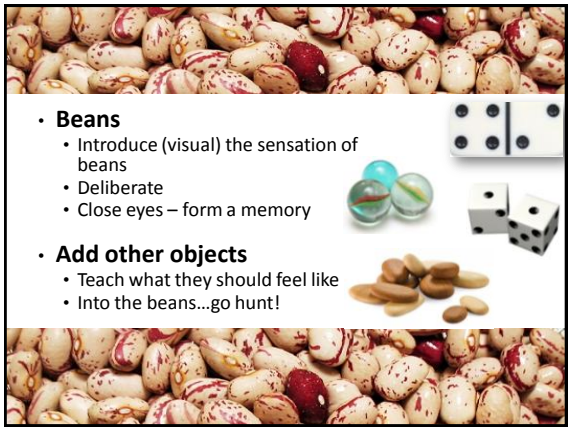

## More advanced

## Phase 5: Now…Mirror Therapy

- If it was only this simple


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## Phase 5: Mirror Therapy

- Using mirrors to trick the brain
- Have to restore L and R first
  - If not – confusion = more pain
- Slowly expose the patient to image

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## Phase 5. The BOX

- Sturdy (use a new box or reinforce)
  - No distortion
- Avoid images/writing on the box
- Perspex mirror (otherwise 7 years of CRPS)
- Cheap

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## Phase 5: Mirror Therapy

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## 5. Principles

- Prepare the patient
  - TNE
  - Emotional
- Sit evenly
- No jewelry
- ? Cover tattoos
- Outside (normal) hand works
  - If bilateral: Least affected = normal side

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## Phase 5: Mirror Therapy – Ideas

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## Phase 5: Mirror Therapy – Ideas

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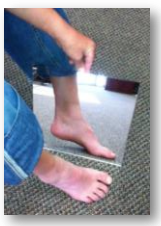
## Mirrors for feet



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## Phase 5: Mirror Therapy – Ideas

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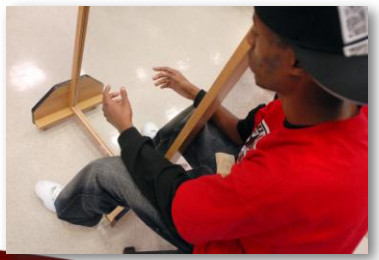
## Phase 5: Mirror Therapy – Ideas



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## Phase 5: Mirror Therapy – Ideas

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## Phase 5: Mirror Therapy - Evidence

- There is good evidence for the use of mirror therapy alone for acute CRPS (McCabe, Haigh et al. 2003; McCabe, Haigh et al. 2004)
- There are case reports of successful mirror therapy management of CRPS (Karmarker and Lieberman 2006) and post hand surgery pain (Rosen and Lundborg 2005).
- Benefits of mirror box therapy with cognitive behavioural therapy demonstrated in three patients with CRPS1. (Vladimir Tichelar, Geertzen et al. 2007)

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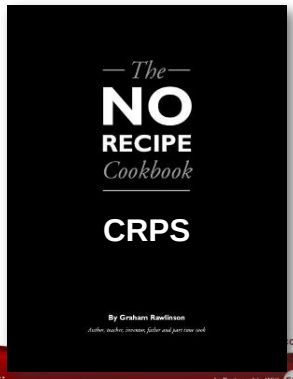
## The CRPS Sequence

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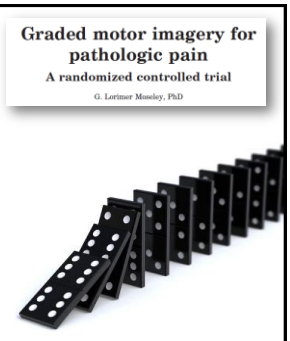
## GMI Sequence

- It works best if carried out in the **sequence** of
  - Laterality recognition
  - Motor imagery
  - Mirror therapy

Moseley GL. Graded motor imagery for pathologic pain: a randomized controlled trial. *Neurology.* Dec 26 2006;67(12):2129-2134.

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## Our Recommendation

Review of the sequence:

1. Therapeutic Neuroscience Education
2. Left/Right Discrimination
3. Motor Imagery
4. Sensory Discrimination, Localization and Graphesthesia
5. Mirror Therapy


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## CRPS Treatment: NOW – The stuff we used to do…

- Therapeutic Neuroscience Education
- Graded Motor Imagery
- Sensory Discrimination
- **Regular Therapy**
  - **Sensory integration**
  - **ROM**
  - **Function**
  - **Etc.**

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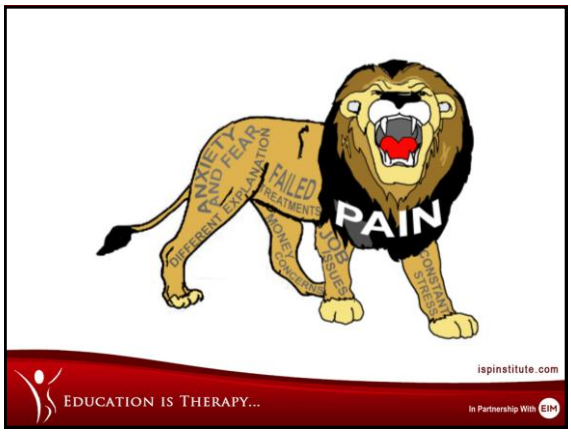
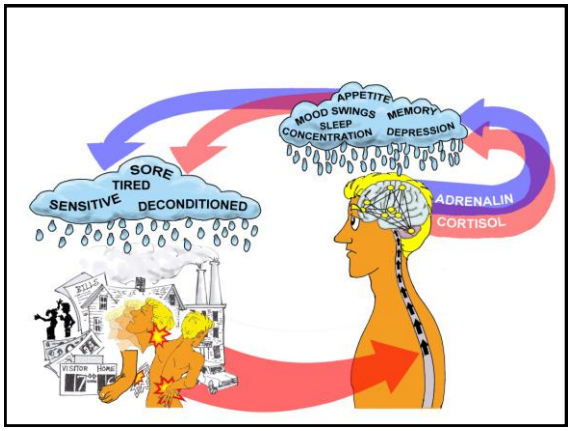
## CRPS Treatment




## Case Study

- 21-year old collegiate soccer player, majoring in education
- Right wrist sprain 5 months ago
- X-rays (-); wore brace x2 weeks
- c/o constant burning pain, 9/10, in hand, wrist and forearm
- Persistent edema, redness
- "Feels like a club, not a hand"
- Poor tolerance to clothing touching wrist/forearm
- Cannot write or type with right UE
- Schoolwork suffering, concerned she will lose scholarship

## Is this CRPS?

**Panel: Budapest diagnostic criteria for CRPS** (Harden, Bruehl et al. 2010)

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three (clinical diagnostic criteria) or four (research diagnostic criteria) of the following categories:
   - Sensory: hyperesthesia or allodynia
   - Vasomotor: temperature asymmetry, skin color changes, or skin color asymmetry
   - Sudomotor or edema: edema, sweating changes, or sweating asymmetry
   - Motor or trophic: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
3. Must display at least one sign at time of diagnosis in two or more of the following categories:
   - Sensory: hyperalgesia (to pinprick) or allodynia (to light touch, deep somatic pressure, or joint movement)
   - Vasomotor: temperature asymmetry, skin color changes or asymmetry
   - Sudomotor or edema: edema, sweating changes, or sweating asymmetry
   - Motor or trophic: decreased range of motion, or motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
4. No other diagnosis better explains the signs and symptoms

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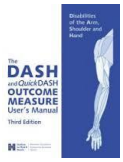
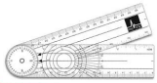
## What will you measure?

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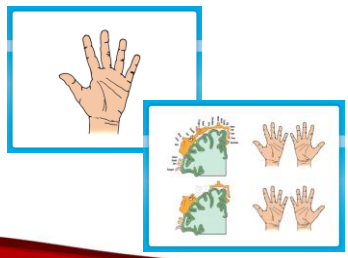
## Treatment: Where will you start?



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## How will you progress?




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## Still too hot to handle, but laterality improving…what next?


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## What else?


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## Last steps…


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## Always keeping in mind:

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## Thank you & acknowledgements…

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- David Butler
- ISPI staff and faculty

International Spine & Pain Institute
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EIM Evidence in Motion
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