



# **Pain in the Brain: The image of pain**

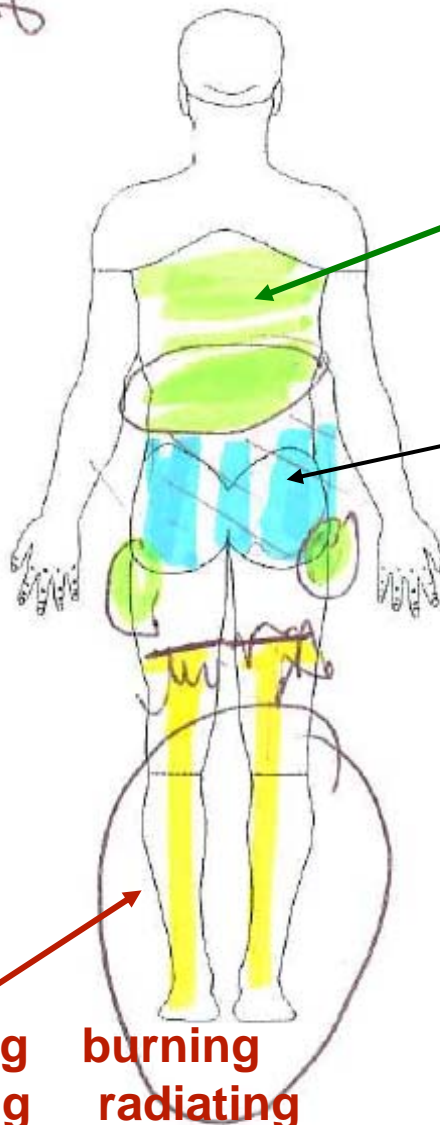
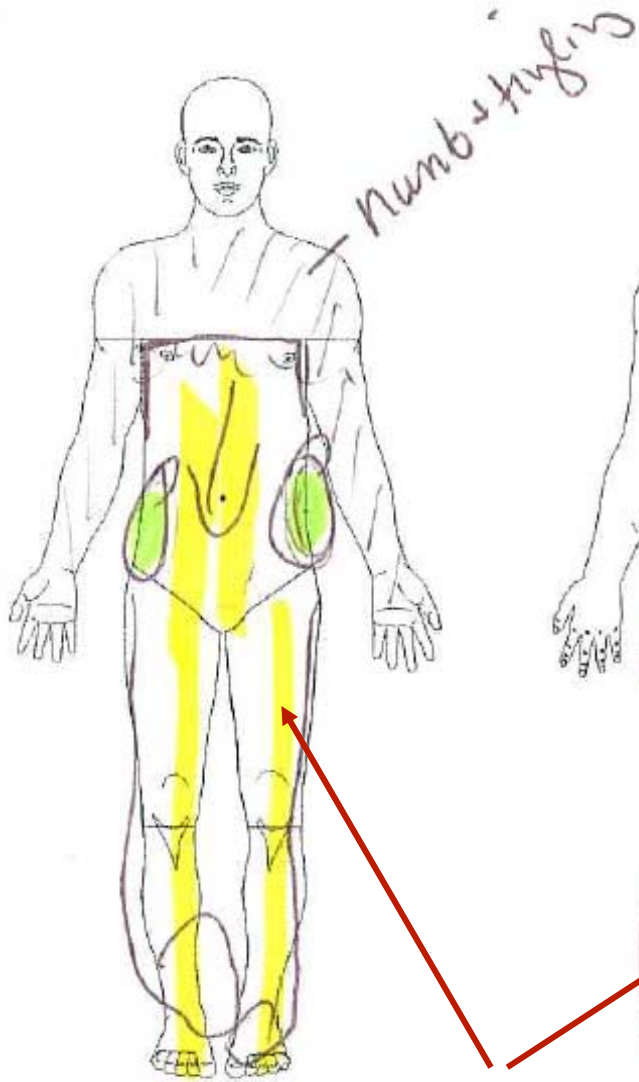
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# The problem

- Störmer et al., 1997 (n=901)  
**66%** chronic pain or dysesthesiae  
>7 on VAS (61%)
- Widerström-Noga et al., 1999 (n=430)  
**77%** reported chronic pain  
>7 on NRS (50 %)
- Turner et al., 2001 (n=384)  
**79%** experienced chronic pain
- Finnerup et al., 2001 (n=330)  
**77%** experienced chronic pain or dysesthesiae  
Median VAS 41
- Rintala et al., 2005 (n=348)  
**75%** reported having at least one pain problem
- Wollaars et al., 2007 (n=279)  
**77%** reported chronic pain

❖ **Chronic refractory pain superimposed over other impairments of SCI further decreases quality of life** (Anson & Shepherd, 1996; Westgren & Levi, 1998).

❖ **After SCI, few pains completely resolve either spontaneously or due to treatment. However, new sources of pain may evolve such as upper extremity pain** (Siddall et al., 2003; Jensen et al., 2005; Cruz-Almeida et al., 2005).




sharp throbbing  
burning penetrating  
aching biting

numb (nonpainful)

sharp pricking burning  
stabbing stinging radiating  
crushing shocking electric

- *Pain Is an Unpleasant Sensory and Emotional Experience Associated With Actual or Potential Tissue Damage, or Described in Terms of Such Damage (IASP, 1979).*
- The complex nature of pain including both sensory and affective components (Melzack & Casey, 1968) suggests that the experience of pain must involve the activation and interaction of multiple areas of the brain.

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- **An increased understanding of how the brain processes SCI-related pain may generate new potential targets for therapeutic interventions.**

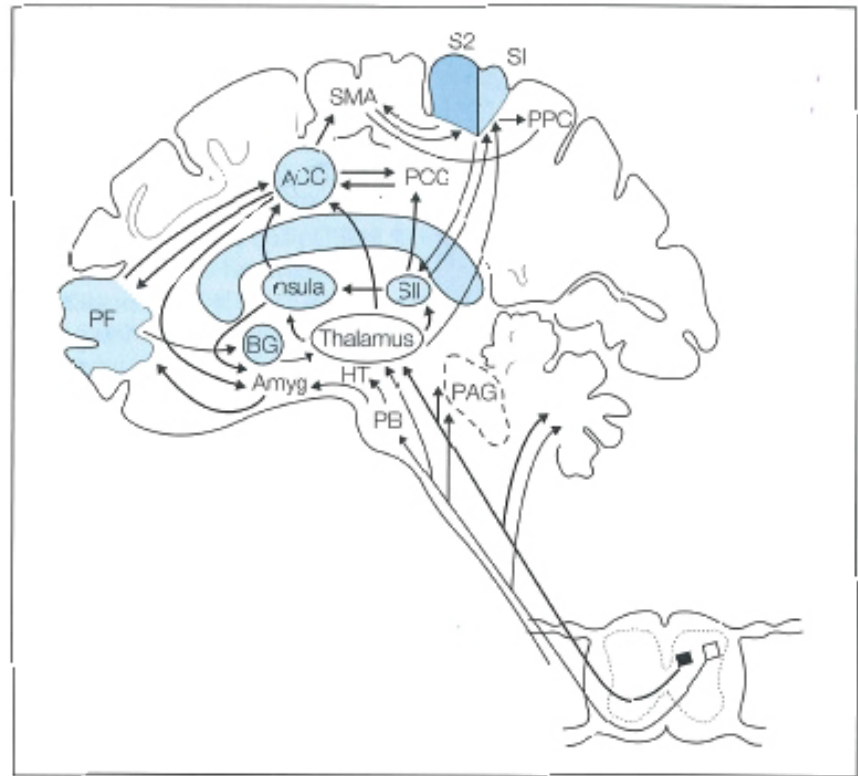
# Areas of the brain shown to be activated during pain

- **Cortical**

- Anterior cingulate cortex
- Primary somato-sensory cortex
- Secondary somato-sensory cortex
- Insular cortex
- Prefrontal cortex
- Motor cortices
- Posterior parietal cortex
- Posterior cingulate

- **Sub-cortical areas**

- Thalamus
- Basal ganglia
- Cerebellum
- Hypothalamus
- Amygdala
- Para brachial nuclei
- Periaqueductal gray



**Fig. 6.2** Schematic representation of ascending pathways, subcortical structures and cerebral cortical structures involved in processing pain. ACC, anterior cingulate cortex; Amyg, amygdala; BG, basal ganglia; HT, hypothalamus; M1, primary motor cortex; PAG, periaqueductal gray; PB, parabrachial nucleus of the dorsolateral pons; PCC, posterior cingulate cortex; PF, prefrontal cortex; PPC, posterior parietal complex; S1 and SII, first and second somatosensory cortical areas; SMA, supplementary motor area. (Adapted from Price 2000.)

# Acute pain processing

## – Somato-sensory cortices (SI and SII)

- Perception of sensory aspects of pain (location, duration).

## – Anterior cingulate cortex (ACC)

- Emotional and motivational aspects of pain
- Hypnotic suggestions for reduction of pain unpleasantness reduced ACC activity (Rainville et al., 1997).

## – Insular cortex (IC)

- Noxious and innocuous temperature (Craig et al., 2000).
- Autonomic control (Oppenheimer et al., 1996).
- Stimulation of the IC produce unpleasant pain (Ostrowsky et al. 2002).



# Acute pain processing

## – Prefrontal cortex

- No systematic relationship with pain intensity (Coghill et al., 1999).
- May be related to cognitive aspects of pain perception, rather than directly to pain sensation or affect.

## – Cerebellum

- Processing and modulation of visceral and somatic nociceptive responses (Saab & Willis, 2001).

## – Thalamus

- Primary relay station for incoming nociceptive input.

# Psychological factors

**Prefrontal cortex**

**Anterior cingulate cortex**

**Insular cortex**

- Anticipation of pain
- Attention, distraction
- Hypnotic suggestions for reduction of pain unpleasantness
- Anxiety
- Placebo responses

# Neuropathic pain

## Increased activity found in:

- Somato-sensory cortices I and II
- Prefrontal cortex
- Thalamus (or decreased)
- Anterior cingulate cortex
- Insular cortex

# MR Spectroscopy

- **MRS** is a non-invasive method to measure metabolites in the human brain.
- **MRS** is based on the fact that different chemicals vibrate at different frequencies when stimulated by a magnet.
- **MRS** produces a signature of the nature and amounts of chemicals that are present in the brain.
- **Stability of signals is an advantage for longitudinal studies or clinical trials.**
- **Changes are reflective of long-term plasticity.**

# Proton Magnetic Resonance Spectroscopy of the Thalamus in Patients With Chronic Neuropathic Pain After SCI.

*Pattany PM, Yezielski, RP, Widerström-Noga EG, Bowen BC, Martinez-Arizala A, Garcia BR, Quencer RM. Am J Neuroradiol 2002;23:901-905.*

- 1.5-T whole-body MR-imaging system.
- Localized proton spectra were acquired from the left and right thalami by using a 8-cm<sup>3</sup> voxel.
- Concentrations for N-acetyl (NA), total Creatine (Cr), Choline compounds (Cho), Glutamate (Glu), Glutamine (Gln), Glu and Gln (Glx), and myo-inositol (Ins).

# Metabolites of interest

- ❖ **N-acetyl aspartate (NAA)** is a free aminoacid thought to be localized in neurons in the brain and commonly considered a neuronal marker and an indicator of neuronal dysfunction.
- ❖ **Myo-inositol (Ins)** is an organic osmolyte, with a major role in the volume and osmoregulation of astrocytes and is considered a glial marker

	<b>Neuropathic pain (n=7)</b>	<b>No neuropathic pain (n=9)</b>	<b>Controls (n=10)</b>
<b>Mean NA (nmol)±SD)</b>	<b>6.05 ± 0.21**</b>	<b>6.66 ± 0.41</b>	<b>6.30±0.35</b>
<b>Mean Ins (nmol)±SD)</b>	<b>2.89 ± 0.70</b>	<b>2.26 ± 0.31</b>	<b>2.66 ± 0.54</b>
<b>NA/Ins ratios ±SD</b>	<b>2.18 ± 0.42**</b>	<b>2.96± 0.47</b>	<b>2.47 ± 0.58</b>

# Results

- Concentration of N-acetyl aspartate was negatively correlated with pain intensity.
- Concentration of *Myo*-inositol positively associated with pain intensity.



- ❖ SCI patients with neuropathic pain had decreased NAA levels compared with control subjects and SCI patients with no neuropathic pain. Low levels of NAA was also associated with higher pain intensity.
- ❖ Ratio (NAA/Ins) was significantly lower in persons with neuropathic pain and elevated Ins levels were associated with higher pain intensity. This is consistent with recent research showing a relationship between glial activation and persistent pain behavior in rats with injury to the spinal cord (Zhao, Waxman, Hains, J Neurosci 2007;27:2357-68).

**A possible explanation may be dendritic pruning, neuronal loss, or dysfunction of inhibitory neurons in combination with glial activation in the thalamus.**

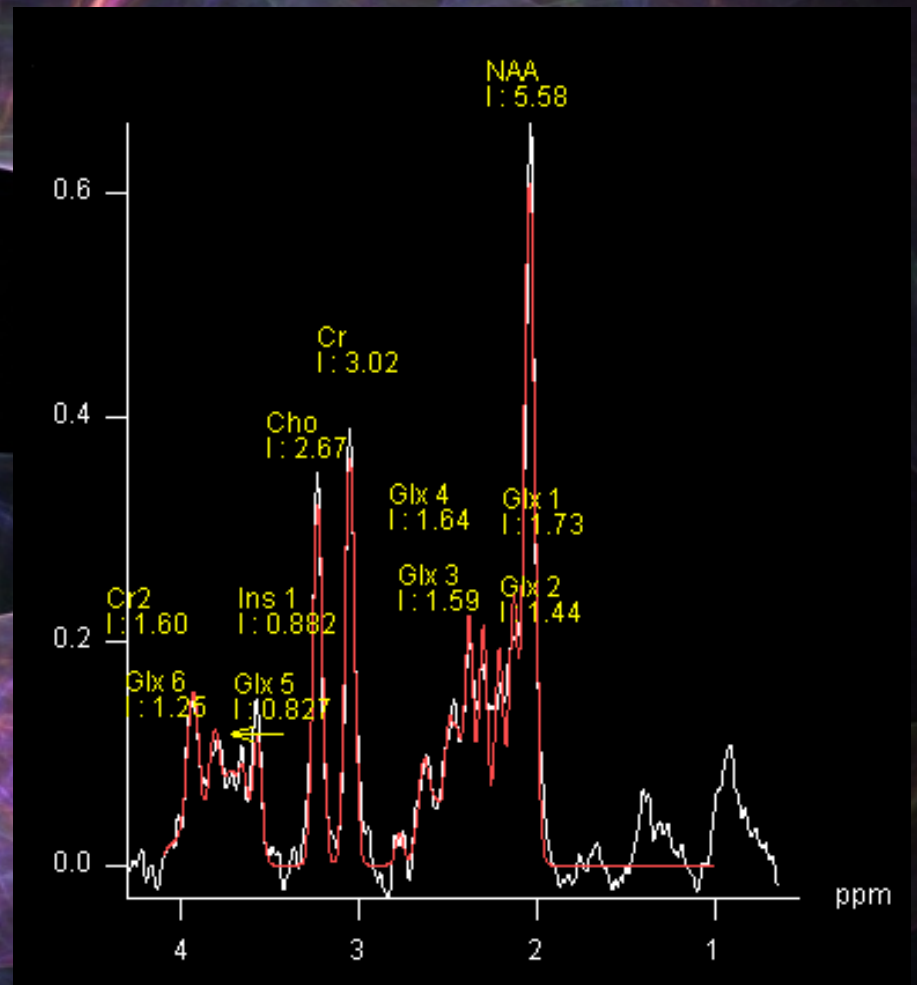
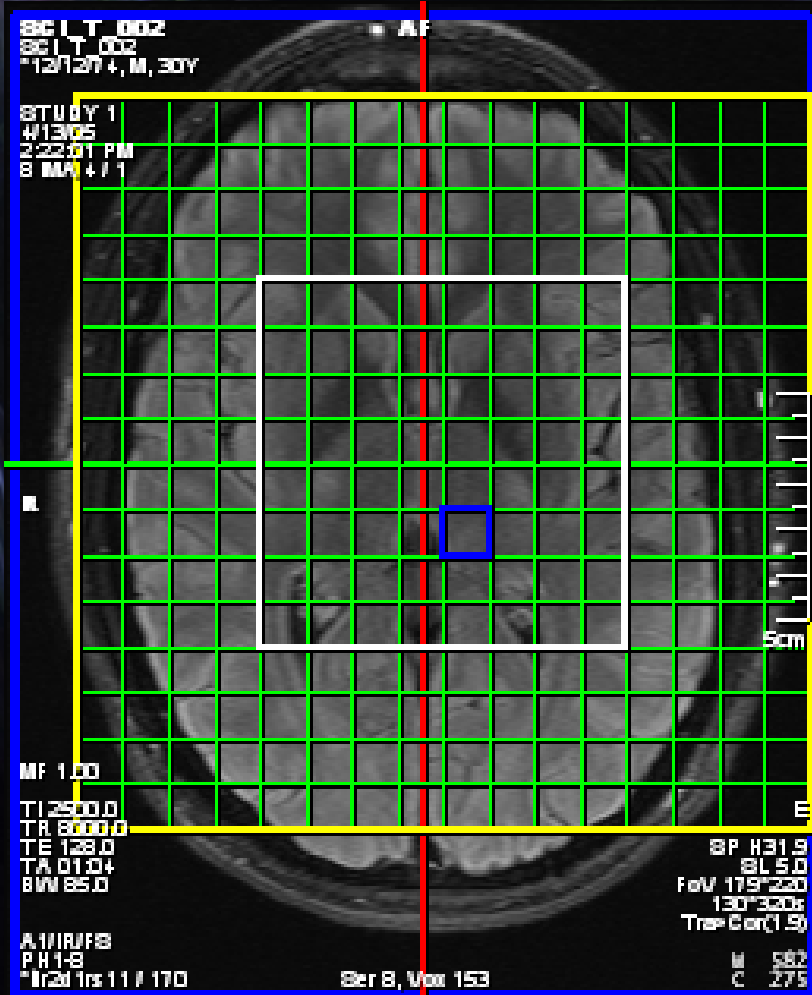
**This dysfunction may result in disinhibition of pain pathways and greater activity of excitatory neurons resulting in a heightened sensation of pain.**

# New MRS study in SCI

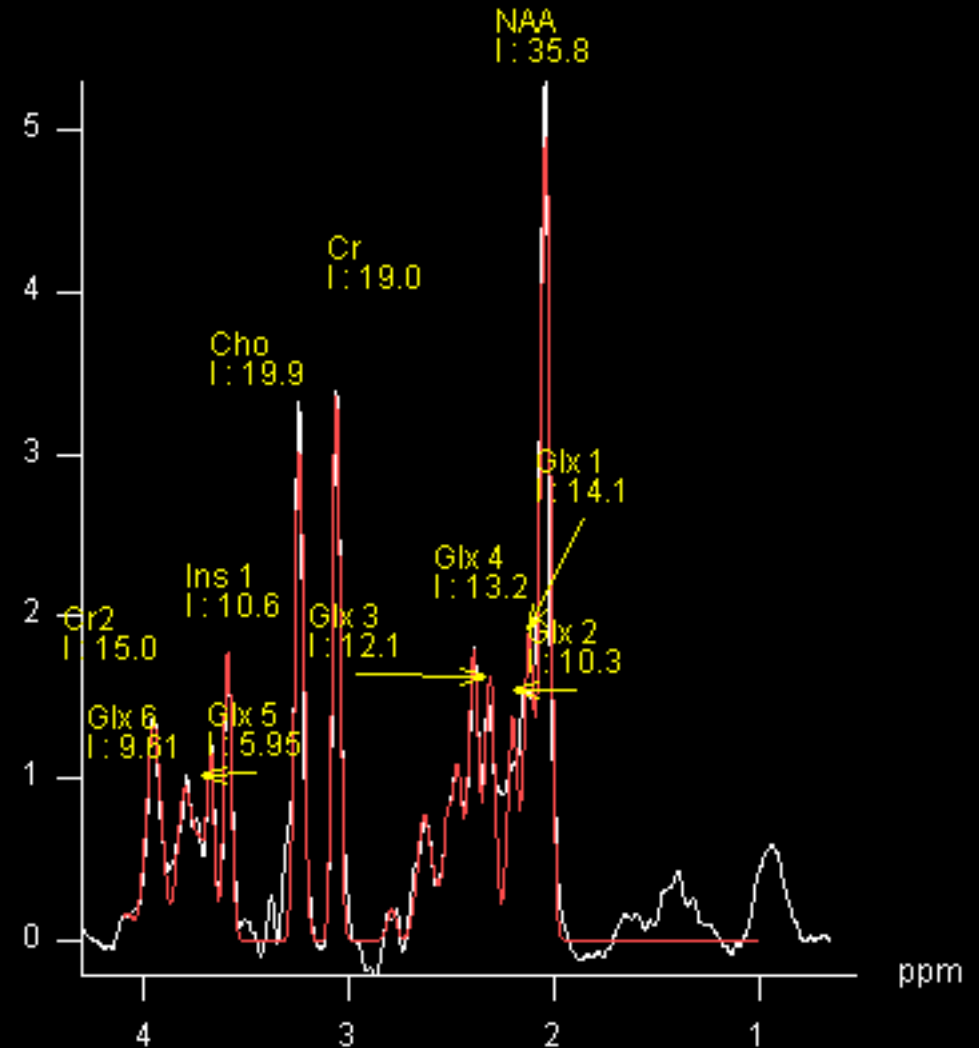
**Co-Investigators:** Pradip Pattany, PhD, Elizabeth Roy Felix, PhD, Alberto Martinez-Arizala, MD, Diana Cardenas, MD, Salome Perez, PhD, Orlando Gómez-Marín, PhD

- 3.0 Tesla provides a higher signal to noise ratio for the spectral data.
- Imaging the anterior cingulate cortex allows us to study the attentional and affective processing of SCI-related pain.
- The pain evaluation (including the quantitative sensory evaluation) is differentiated, allowing us to analyze the different pains separately.
- Imaging the Thalamus and the ACC will allow us to better understand the role of metabolic processes in this areas and their relationships with psychosocial factors and neuropathic pain in SCI.

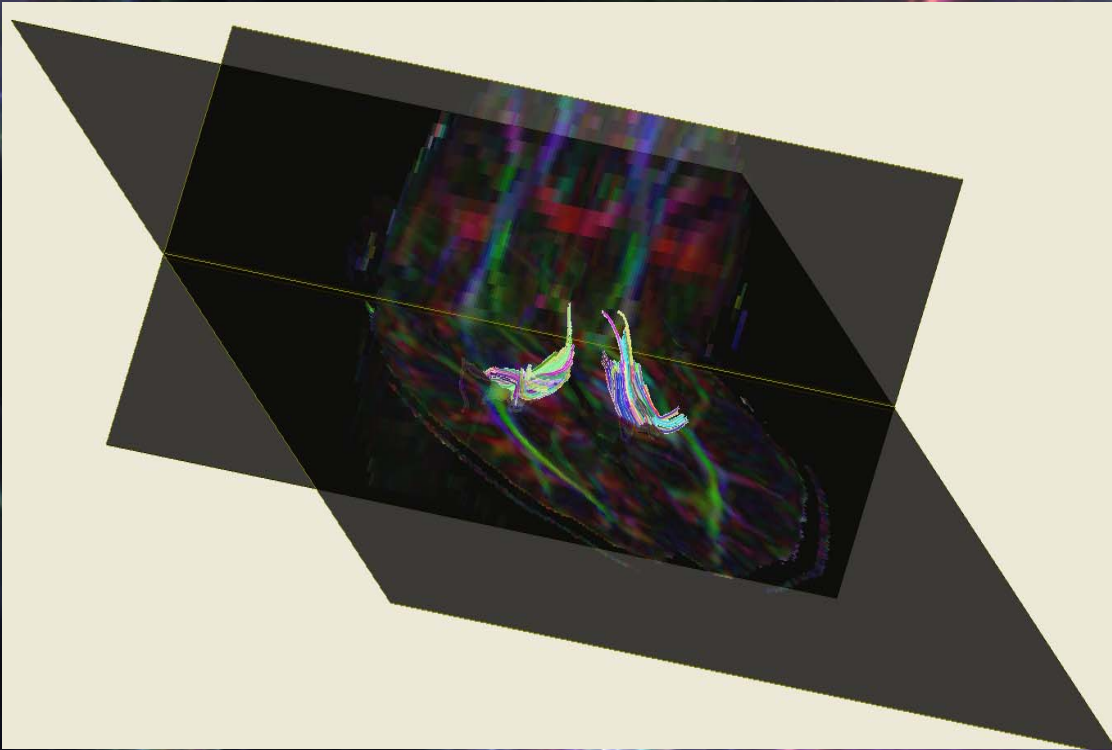
# Thalamus



# Anterior cingulate cortex



# Diffusion Tensor Imaging (DTI)



- *DTI image with color coded direction map and with fiber tracking in the region of the thalamus*

- **Chronic pain associated with SCI is both heterogeneous and refractory.**
- **Multiple pathophysiological and psychological mechanisms are responsible for the origin and maintenance.**
- **With the goal of tailored mechanism-based treatments, specific pain generating mechanisms need to be identified in each person and treatment targeted to these.**