Neural Correlates of Ongoing Chronic Low Back Pain as Measured by Arterial Spin Labeling (ASL)

Marco L. Loggia, PhD
Outline of the talk

• Chronic Low Back Pain
• Imaging the brain in pain
• Intro to Arterial Spin Labeling
• Studying CLBP with ASL
• Conclusions
Chronic Low Back Pain

• Low back pain is the fifth most common reason for all physician visits in the USA and a leading cause of disability.
• In 85% of the individuals reporting back pain, no definitive diagnosis can be made (Cavanaugh and Weinstein, 1994; Devo, 1998)
• The proportion of people who self-report to have low back pain that interferes with their daily functioning is ~25%
• Low back pain is the fifth most common reason for all physician visits in the USA and a leading cause of disability.
Chronic Low Back Pain

- Even when anatomic abnormalities are detected, the significance is unclear

L5-S1 disc protrusion in a 24-y.o. woman with no back pain


➢ The identification of biomarkers for CLBP would have significant clinical implications.
Why looking into the brain?

• Most of the research on chronic pain to date is at the spinal cord level

• But… structural and neurochemical changes have been reported in pain patients

Apkarian et al., JNeurosci 2004
Seminowicz et al., Gastroenterol 2010
Harris et al., Arthritis Rheumat 2009

See also Kuchinad et al., JNeurosci 2007; DaSilva et al., PLoS 2008, etc
Imaging brain responses to pain
Imaging brain responses to pain

Apkarian et al 2005
Imaging brain responses to pain

This type of design highlighted the occurrence of augmented central pain processing in patients with chronic pain.

For instance, the application of the same stimulus to LBP or FM was associated with stronger and more extended activations than in HC (e.g., Giesecke et al., Arthritis Rheum, 2004)

But how can we study CLINICAL pain?
From experimental to clinical pain

• Most of experimental pain is brief/cutaneous, whereas clinical pain (CP) is deep and prolonged.

• Furthermore, normally CP cannot be switched on and (especially) off at will

→ CP tends to elude study with block or event-related experimental paradigms and BOLD imaging

Apkarian et al., Neurosci Letters, 2001
Alternative approaches to the ‘two-state subtraction’ designs

- Correlating the online temporal profile of pain with BOLD signal

Baliki, JNeurosci 2006
Alternative approaches to the ‘two-state subtraction’ designs

• Resting state connectivity analyses

Napadow et al., Arthritis Rheum 2010
Another alternative: ‘two-state subtraction’ design with Arterial Spin Labeling (ASL)
Arterial spin labeling (ASL) is a family of MRI techniques which use water in arterial blood as a freely diffusible tracer to measure perfusion noninvasively.

Arterial blood is tagged by saturating/inverting the longitudinal component of the MR signal.

Once in the capillaries, the tagged water passes into the brain tissue, where it alters the local tissue’s longitudinal magnetization.

Interleaved with the ‘tag images’ are usually ‘control images’, in which the magnetization of arterial blood is fully relaxed.
Arterial spin labeling

- Of the sequences available at MGH, the Siemens-supported sequence is **ep2d_pasl**, a PICORE-Q2TIPS sequence.

- ‘Tag’ images are acquired by labeling a thick inversion slab (~10cm), proximal to the imaging slices; ‘Control’ images are acquired by applying an off-resonance inversion pulse without any spatial encoding gradient.

Luh et al., Magn Reson Med, 1999
**Arterial spin labeling**

- Subtraction of the labeled ("tag") image from a reference ("control") image produces a perfusion-weighted image, which is proportional to CBF

Liu and Brown, J Int Neuropsych Soc 2007
The perfusion-weighted images can be further processed to obtain quantitative CBF map, in absolute units (in ml/100g/min).

Arterial spin labeling

\[ f = \frac{\lambda \Delta M}{2 \alpha m_0 T_1 \exp(-T_1/T_1')} \]

Equation from JJ-Wang et al. JMRI 18:404-413, 2003
Arterial spin labeling

- Cross-validation studies, and clinical applications

\[ H_2^{15}O \text{ PET} \quad \text{ASL} \]


\[ y = 0.72x - 3.76 \quad \chi^2 = 0.52 \]


Hypoperfusion in an acute stroke

Hyperperfusion in a glyoblastoma

John Detre, MAGNETOM Flash 2008
Rationale of the study

• Although CP cannot be easily turned off at will, it is possible to increase it by opportune manipulations.

• We hypothesized that:
  – An increase in ongoing pain will be associated with an increase in rCBF in brain areas involved in central pain processing
  – As ASL allows the quantification of CBF, this technique will allow to detect these changes.
Participants

- 16 patients suffering from discogenic low back and radicular pain for more than six months.

- 16 age- and gender-matched healthy controls

<table>
<thead>
<tr>
<th>Gender</th>
<th>Patient/ctrl</th>
<th>N</th>
<th>Age mean</th>
<th>Age StDev</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>Patient</td>
<td>11</td>
<td>49</td>
<td>13.5794</td>
</tr>
<tr>
<td>F</td>
<td>Control</td>
<td>11</td>
<td>48.27273</td>
<td>12.07552</td>
</tr>
<tr>
<td>M</td>
<td>Patient</td>
<td>5</td>
<td>44.2</td>
<td>15.43373</td>
</tr>
<tr>
<td>M</td>
<td>Control</td>
<td>5</td>
<td>43.2</td>
<td>13.14154</td>
</tr>
</tbody>
</table>
Imaging acquisition and analyses

- 6 minutes **pulsed ASL** scans were collected using the “PICORE-Q2TIPS” MRI labeling method with a 3 T Siemens TIM Trio MRI System, equipped with a 32-channel head coil (TR/TE/TI1/TI2= 3000/13/700/1700ms; Thickness of labeling region =110mm, Gap=21.1mm).

- Voxel size: 3.5x3.5x6.25; 16 slices

- Control and Tag images were motion corrected, surround subtracted and then further processed to obtain quantitative CBF maps.

- CBF maps were interpolated onto Freesurfer-reconstructed surfaces, and then smoothed with a kernel of ~7mm (2*voxel size)

- Changes in CBF were computed for each subject, interpolated onto standard space (fsaverage) and then group-averaged

- Montecarlo simulations run to correct for multiple comparisons (vertex threshold of p=0.01)
Results

Clinical maneuvers were painful for patients, but not for the controls. Noxious heat elicited ratings which approximated the pain severity evoked by clinical maneuvers.

In patients, clinical maneuvers, but not heat, induced a clinically significant increase in ongoing pain (>30%)
Results

Estimated average CBF yielded physiologically plausible values

No CBF differences were observed between patients and controls at baseline

Ye et al., 2000
After the (painless) clinical maneuvers, controls did not exhibit any increase in the rCBF
Results

Similarly, after the heat pain (which did not cause a clinically significant increase in pain) patients did not exhibit any increase in the rCBF.
Results

However, after the pain-worsening clinical maneuvers, patients exhibited rCBF increases, over a widespread network of areas.
Results

These areas included:

**Primary and secondary somatosensory cortices.** Among the structures most commonly activated in pain imaging studies, are thought to encode the sensory components of pain.

S1 active at the level of the paracentral lobule (sensorimotor representation of the leg)
Results

Right anterior insula. Another very commonly activated region in pain studies, believed to be involved in encoding sensory and/or affective components of pain, as well as in interoception.
Both insula and S2 have been implicated in idiopathic pain conditions, such as fibromyalgia.
Results

Dorsolateral prefrontal cortex. Region which have been found to be hypotrophic in patients with chronic low back pain (Apkarian et al., 2006)
Results

**Medial prefrontal cortex.** Areas which have been implicated in both low back pain (Baliki et al., 2006) as well as in rheumatoid arthritis (Schweinhardt et al., 2008)
Superior parietal lobule. Implicated in attentional mechanisms, and not very often seen active in pain studies. Heightened vigilance to clinical symptoms?
The average rCBF increase caused by the clinical maneuvers was \(~6\text{ml/100gr tissue/min}\)
Delta CBF after clinical maneuvers: Raw values
Conclusions

- Exacerbation of clinical pain is associated with the CBF increase in a widespread network of areas, including areas of the ‘evoked pain matrix’ (anterior insula, S1, S2), and regions less commonly seen active in experimental pain studies (e.g., SPL).

- These findings further support the notion that chronic pain states affect central pain processing.

- ASL is a promising tool to investigate the neural processing of CP, and provides a step forward in the quest for objective biomarkers of CP.

- More in general, ASL appears to be a useful complement to BOLD fMRI imaging in the study of brain function, as it can be successfully applied in designs in which BOLD is suboptimal.
Thanks to…

- Ajay Wasan
- Randy Gollub
- Li Chen
- Jean Chen
- Vitaly Napadow
- Div Bolar
- Doug Greve
- Jian Kong
- Garth Coombs