Predictors and a signature of Chronic Pain

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PRF, NIH, DC
Acute to chronic pain

Cartesian view, 1644

Cortical plasticity

Spinal Sensitization

End Organ Afferents

Cartesian view, 1644

mPFC

[ -36 44 18 ]

End Organ Afferents

Stimulus | Representative receptor
---------|-----------------------
NGF      | TrkA, BK2, 5-HT3, P2X7, ASIC3/V1R1, PGE2/CB1VR1, VR1/VR1-1, DEG/ENaC
Bradykinin| 5-HT, ATP, H+, Lipids, Heat, Pressure
The CRITICAL question

- End organ MRI predicts only 1% of chronic back pain
- Brain imaging studies are all cross-sectional

The critical question is:

Only a small proportion of subjects with a similar injury develop chronic pain.

Why? How?
Transition from acute to chronic back pain

A longitudinal and cross-sectional, observational study.

Recruit subjects with acute back pain of 4-12 weeks, with no history of back pain in prior one year, and with back pain >5/10 at entry.

For one to three years monitor brain parameters.

As back pain patients transition to either recovery or to chronic pain,

What is the role of the brain?
Persisting (SBPp) (no change in pain)

Recovering (SBPr) (>20% decrease in pain)

Consequences

Predictors
Clinical pain parameters with transition to chronic pain

![Graph showing pain intensity over time](image)

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBPp</td>
<td>SBPr</td>
<td>SBPp&gt;SBPr</td>
</tr>
<tr>
<td>VAS (0-100)</td>
<td>54.1±5.0</td>
<td>51.4±4.2</td>
<td>0.42</td>
</tr>
<tr>
<td>MPQ sensory</td>
<td>11.9±1.7</td>
<td>9.2±0.9</td>
<td>1.42</td>
</tr>
<tr>
<td>MPQ affective</td>
<td>3.3±0.6</td>
<td>1.6±0.4</td>
<td>2.09*</td>
</tr>
<tr>
<td>MPQ radiculopathy</td>
<td>5.2±0.5</td>
<td>4.1±0.4</td>
<td>0.46</td>
</tr>
<tr>
<td>NPS</td>
<td>38.6±5.1</td>
<td>36.2±2.6</td>
<td>1.34</td>
</tr>
<tr>
<td>BDI</td>
<td>6.4±1.0</td>
<td>6.7±1.3</td>
<td>-0.83</td>
</tr>
<tr>
<td>PANAS positive</td>
<td>33.4±1.7</td>
<td>29.1±2.5</td>
<td>1.41</td>
</tr>
<tr>
<td>PANAS negative</td>
<td>22.5±2.6</td>
<td>22.7±3.1</td>
<td>-0.05</td>
</tr>
</tbody>
</table>

![Table showing comparison between Visit 1 and Visit 4](image)

<table>
<thead>
<tr>
<th></th>
<th>Visit 4</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBPp</td>
<td>SBPr</td>
<td>SBPp&gt;SBPr</td>
</tr>
<tr>
<td>VAS (0-100)</td>
<td>58.9±5.1</td>
<td>17.2±3.4</td>
<td>6.73**</td>
</tr>
<tr>
<td>MPQ sensory</td>
<td>13.3±1.3</td>
<td>4.8±1.2</td>
<td>4.50**</td>
</tr>
<tr>
<td>MPQ affective</td>
<td>3.5±0.8</td>
<td>0.9±0.4</td>
<td>2.66*</td>
</tr>
<tr>
<td>MPQ radiculopathy</td>
<td>5.2±0.6</td>
<td>3.9±0.4</td>
<td>2.65*</td>
</tr>
<tr>
<td>NPS</td>
<td>44.9±2.1</td>
<td>14.2±1.9</td>
<td>5.91**</td>
</tr>
<tr>
<td>BDI</td>
<td>9.3±2.1</td>
<td>3.8±0.8</td>
<td>2.02</td>
</tr>
<tr>
<td>PANAS positive</td>
<td>32.5±1.7</td>
<td>35.4±1.6</td>
<td>1.17</td>
</tr>
<tr>
<td>PANAS negative</td>
<td>20.4±1.7</td>
<td>14.4±1.1</td>
<td>2.98**</td>
</tr>
</tbody>
</table>
Baseline | Acute | Sub-acute | Chronic
--- | --- | --- | ---
visit 1 | visit 2 | visit 3 | visit 4
| time 0 | 7 weeks | 30 weeks | 55 weeks

Functional connectivity

Post-hoc

Unbiased

SBPr SBPp
Activation of Corticostriatal Circuitry Relieves Chronic Neuropathic Pain

Lee et al.,
J Neuroscience, April 1, 2015
White matter differences at baseline distinguish SBPp from SBPr

A

Pain (VAS)

Time (weeks)

Visit 1 Visit 2 Visit 3 Visit 4

SBPp

SBPr

B

Time (weeks)

SBPp SBPr

ns

C

x = -16

x = -39

z = +26

z = +5
Baseline | Acute | Sub-acute | Chronic
--- | --- | --- | ---
visit 1 | visit 2 | visit 3 | visit 4
| time 0 | 7 weeks | 30 weeks | 55 weeks

**Functional connectivity**

- **mPFC** (2, 52, -2)
- **NAc** (10, 12, -8)

**White matter diffusivity**

- SBPr
- SBPp
Tracking pain chronification in the full cohort of SBP and for a subgroup for up to 3 years.
Limbic-brain white matter network clusters to 3 communities: mPFC-Nac-Amy white matter and functional connectivity distinguishes SBP groups

mPFC-Nac-Amy WM network

mPFC-Nac-Amy Func Network
Hippocampus size is larger in subjects where back pain recovers (SBPr) and constant over 3 years.
Amygdala size is larger in subjects where back pain recovers (SBPr) and constant over 3 years.
Amygdala and hippocampus shape differences are seen between SBPp and SBPr, persistently.
Persisting (SBPp)  
Recovering (SBPr)  

Predictors  
mPFC-Nac-Amy  
FC  WM  Size  

Acute  Sub-acute  Chronic

visit 1  visit 4  
time 0  55 weeks  

Visit timeline and predictors for different stages of recovery.
Full model for predicting development of chronic pain at 1 year based on brain values observed within weeks after start of back pain

Model prediction is ~90% correct

Mu-opiate gene contribution is ~ 5% of variance

Outcome: $r^2 = 0.89$
Full model for predicting development of chronic pain at 1 year based on brain values observed within weeks after start of back pain.

**Model prediction is ~85% correct**

Depression contribution is ~3% of variance.
PREDICTING intensity of back pain at 1 year based on parameters observed within weeks after start of back pain

Model prediction is now only ~40% correct

Brain contribution is ~ 10% of variance

Brain

White matter
mPFC-amy-Nac

SBPr(25) SBPp(30)

Functional
mPFC-amy-Nac

Right Amygdala
Volume

-0.35

Injury

Pain Week 0

0.47

Pain Week 56

Gene

rs678849

Outcome: r^2 = 0.42

Prediction is poor and dominated by pain at entry into study
Can we identify a signature of chronic pain common across conditions and species?

Analysis of resting state fMRI regarding network graph properties:

Chronic pain is characterized by a global disruption of information sharing.
Resting state brain networks: undirected functional connectivity

Generate link maps for patients & controls
Contrast them as a function of number of links
Basic elements of a graph

Degree = 4

Bullmore, E.T. & Sporns, O. 2012
Deriving $Kd$: a global network measure of rank order disruption

Mean control = 150 OFF-SITE subjects from NITRC connectome1000
$K_d$ is about -0.3 in chronic pain patients and related to pain intensity (at link density of 10%)
$K_d$ emerges in time during transition to chronic pain

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Sub-acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6 months</td>
<td>1 year</td>
<td></td>
</tr>
</tbody>
</table>

**Graphs:**

- **Graph a:**
  - Title: Pain intensity (VAS)
  - Data points for SBP (n = 12) and Healthy (n = 22).

- **Graph b:**
  - Title: $K_D$
  - Data points for Visit 1, Visit 2, Visit 3.

- **Graph c:**
  - Title: Degree (Group - Control)
  - Data points for Visit 1, Visit 2, Visit 3.

- **Graph d:**
  - Title: $K_D$ (Visit 1 - Visit 3)
  - Correlation coefficient: $R = -0.80$, p < 0.01.
$Kd$ emerges in time in rats after a neuropathic injury.
Four distinct stages for chronic pain

1. Predisposition
2. Injury
3. Transition
4. Maintenance …

WM vulnerability
Limbic Structures + Genes
Cortical reorganization
Emotional pain state
Rank order disruption

mPFC-NAc

3 = 1 + 2 + mesolimbic learning
• Brain characteristics determine propensity for chronic pain. Therefore, it is a NEUROLGICAL vulnerability.

• Chronic pain state globally disrupts information flow/sharing in the brain
  • in proportion to the intensity of the pain,
  • commonly across types of chronic pain,
  • and even in anesthetized neuropathic rats.

• Chronic pain is a brain “network disease” state of decreased segregation and increased randomization.
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Chronic Pain

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