Imaging glial activation in human pain disorders

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Hundreds of animal studies implicate *glial cells* in pain

- Microglia and astrocytes ‘activate’ in animal models of pain
- Activated glia produce cytokines and other pro-inflammatory mediators
- Inhibition of glial activation inhibits/reverses pain
This is a world-wide effort

USA
L. Watkins - J. Deleo - R.R. Ji
P. Dougherty - S. Carlton - G. Gebhart
C. Woolf - A. Basbaum
K. Ren - R. Dubner - T. Yaksh
E. Milligan - S. Waxman - H.R. Weng
C. Hulsebosch - D. Fink
P. Mantyh - L. Jasmin - R. LaMotte
F. Wei - S. Tang - E. Romero-Sandoval
P. Haydon - K. McAuthor - T Berta - C. Cahill

Canada
M. Salter - Y. De Koninck - J. Mogil;
J. Zhang - B. Sessle - G. Bennett

UK
S. McMahon
M. Malcangio
D. Bennett
S. Beggs
A. Rice
M. Fitzgerald

Germany
R. Kuner, C. Sommer

Switzerland
I. Decosterd / M. Suter

Israel
M. Hanani

China
Y.Q. Zhang
Z.Q. Zhao
Y.G. Gao
X.G. Liu
W. You
Y.C. Li

Korea
S.B. Oh
S. Lee

Japan
Inoue / Tsuda
K. Noguchi
K. Iwata

Taiwan
Y.R. Wen
C. Wong

Australia
M. Hutchinson

PubMed Search for Glia and Pain

All around the world …

Slide courtesy of Ru-Rong Ji (modified)
Do glial cells have a role in human pain?

- Hundreds of animal studies implicate glial cells in pain
  - Microglia and astrocytes ‘activate’ in animal models of pain
  - Activated glia produce cytokines and other pro-inflammatory mediators
- Inhibition of glial activation inhibits/reverses pain

Tsuda et al., Nature 2003
Gao and Ji, Neurotherapeutics 2010

http://www.atlantapainmanagementcenters.com
Can we “see” glial activation in vivo?

- Post-mortem studies in the human spinal cord
  - Complex Regional Pain Syndrome (Del Valle et al., Brain Behavior and Immunity 2009)
  - HIV neuropathy (Shi et al., J Neurosci 2012)
The Translocator protein (18 kDa) (TSPO)

- A five transmembrane domain protein mainly situated in the outer mitochondrial membrane
- Involved in steroid hormone synthesis (Fan et al., PNAS 2015)
  - however see Banati et al., Nat Commun 2014

Rupprecht et al., Nature Rev Drug Discov 2010
TSPO as a marker of glial activation

- Very low basal expression in the healthy CNS
- Upregulated by activated microglia and astrocytes
  - Experimental autoimmune encephalomyelitis
  - Multiple sclerosis
  - HIV encephalitis
  - Ischemia
  - Alzheimer’s Disease
  - Animal pain models
  - etc

Spinal nerve ligation (rat)

Wei et al., J Neurosci 2013
Liu et al., Pain 2016
TSPO as a marker of glial activation

TSPO can be imaged in vivo using PET (Albrecht et al., ACS Chem Neurosci 2016)

[¹¹C]PK11195
- Prototypical ligand
- Low specific-to-nonspecific binding ratio

[¹¹C]PBR28
- Second generation ligand
- 80-fold higher specific binding in primate brain (Kreisl et al., Neuroimage 2010)
[\textsuperscript{11}C]PBR28 as a sensitive TSPO ligand

Ischemic stroke (rat model)

Huntington’s disease

Amyotrophic Lateral Sclerosis

Multiple sclerosis

Lois et al., in preparation (Diana Rosas / Jacob Hooker’s labs)

Zurcher, Loggia et al., Neuroimage Clin 2015
TSPO…

- is upregulated in activated glial cells
- can be imaged with PET using $[^{11}\text{C}]$PBR28

Do chronic pain patients demonstrate glial activation, as assessed by increased $[^{11}\text{C}]$PBR28 binding?
Evidence for brain glial activation in chronic pain patients

Marco L. Loggia,1,2,* Daniel B. Chonde,1 Oluwaseun Akeju,3 Grae Arabasz,1 Ciprian Catana,1 Robert R. Edwards,2,4 Elena Hill,5 Shirley Hsu,1 David Izquierdo-Garcia,1 Ru-Rong Ji,2,6 Misha Riley,1 Ajay D. Wasan,2,4,7 Nicole R. Zürcher,1 Daniel S. Albrecht,1 Mark G. Vangel,1 Bruce R. Rosen,1,8 Vitaly Napadow1,2,9 and Jacob M. Hooker1
**Methods**

**Matched-pairs design**

- 19 cLBP patients + 25 controls initially enrolled
- 9 matching-pairs identified, matching for:
  - sex
  - age
  - Ala147Thr polymorphism in the TSPO gene
    (Owen et al., J Cereb Flow Metab 2012)

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**Diagram:**

- cLBP
- controls
- Female 52 y.o. Ala/Ala
- Female 52 y.o. Ala/Thr
- Female 52 y.o. Ala/Ala

unpublished data
Methods

- Integrated PET/MR scanning
- Up to 15 mCi of $[^{11}\text{C}]\text{PBR28}$
- Standardized Uptake Values, normalized by whole brain (SUVR)
- Pain levels and blood levels of cytokines (IL-6, IL-1$\beta$, TNF-\(\alpha\))

Albrecht et al., in preparation
Group differences

Loggia et al., Brain 2015
Individual data

Median cLBP image (n=10)

thalamus

Individual data

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controls

matching pair 0.5 1.6
Test-retest reliability

Same patient, scanned twice 3.5 months apart

Loggia et al., unpublished
Is glial activation in S1/M1 somatotopically organized?

- Paracentral lobule
- Postcentral gyrus

Pain fMRI studies

- Leg pain
  Loggia et al., Pain 2012

- Lumbar pain
  Kim et al. (Napadow lab), in preparation
Regression analyses

![Graphs showing correlation between pain at scan and SUVR values](image-url)
TSPO knock-down: ↑ inflammation

TSPO overexpression ↓ Inflammation

TSPO agonists: allodynia & hyperalgesia

TSPO appears to limit the magnitude of inflammatory responses after their initiation.
Spinal glial activation
(collaboration with Yi Zhang, MD, PhD)

Albrecht, et al (in preparation)

![Image of spine MRI with T11-T12 cord highlighted]

**T11-T12 Cord SUVR**

- **Controls** (n=4)
- **Sciatica** (n=9)

[Graph showing SUVR values for different groups]

Albrecht, et al (in preparation)
Conclusions

- Chronic pain patients demonstrate **TSPO elevations** in brain and (possibly) spinal cord.

- Since TSPO is a marker of glial activation, this suggests that human **chronic pain** is accompanied by glial activation.

- Glial activation may represent a **therapeutic target** for chronic pain, as predicted by animal studies.
Questions/Future directions

- Do other pain conditions also demonstrate TSPO upregulation?
- Do different pain disorders have different ‘glial signatures’?
- Can glial inhibitors and TSPO ligands be used to treat clinical pain?
- Can glial imaging predict who develops chronic pain?
Thanks to...

- Jacob Hooker
- Daniel Albrecht
- Grae Arabasz
- Nazem Atassi
- Vanessa Barth
- Ciprian Catana
- Daniel Chonde
- Rob Edwards
- Doug Greve
- Nicolas Guehl
- Elena Hill
- Shirley Hsu
- David Izquierdo-Garcia
- Ru-Rong Ji
- Oluwaseun Johnson-Akeju
- Jieungchan Kim
- Patti McCarthy
- Norman Kettner
- Ishtiaq Mawla
- Vitaly Napadow
- Marc Normandin
- Ekaterina Protsenko
- Misha Riley
- Bruce Rosen
- Adam Schwartz
- Sergey Shcherbinin
- Mark Vangel
- Ajay Wasan
- Dustin Wooten
- Marlene Wentworth
- Yi Zhang
- MGH Clinical Research Center