A Retrospective of “Advances through Imaging: Signatures of Pain Disease and Recovery”

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Similarly there is evidence that central nervous system pathways have specialized functions that play a role in pain mechanisms.
Imaging Pain In North America

Atlas, Baliki, Bajic, Younger, DaSilva, Hubbard, Linnman, Loggia, Simons, and Many Others
Normal Brain

Chronic Pain Brain

Altered Brain Chemistry
Decrease in Gray Matter Volume in DLPC
Structural Changes in Nerve Tracts

Altered Brain Network Connectivity

Altered Behaviors
Sensory (e.g., spontaneous pain at rest)
Affective (e.g., anxiety, depression, suicide, addiction)
Cognitive (e.g., decreased attention)
Emotional (e.g., reward deficit state)
What are we doing for the Patient?
CNS Neurobiology

Sensory
Emotional
Modulatory

Drug Effects
Genetic Effects
CNS Pathways
Animal-Human Transl.

Drug Devel.
Early Phase Evaluation
Circuit Based Function
New uses for Drugs
Depression Anxiety

Co-morbid Disease
Disease Plasticity

Altered Circuits
Temporal Changes
Altered Function

Surrogate Models
Human Models
Animal Models

Biofeedback
Placebo Response

Functional genomics

fMRI

Drugs

Applied Biology and Pharmacology

Therapies

CNS Disease Process

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Sensory and Affective Components Of Pain

Multiple representations of pain in human cerebral cortex.
Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH.

Pain affect encoded in human anterior cingulate but not somatosensory cortex.
Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC.

Cognitive and emotional control of pain and its disruption in chronic pain.
Bushnell MC, Ceko M, Low LA.

2013

Attentional and emotional factors modulate pain perception via different pathways

1997

1991
Mapping a Sensory Pathway

**Somatotopic activation in the human trigeminal pain pathway.**
DaSilva AF, Becerra L, Makris N, Strassman AM, Gonzalez RG, Geatrakis N, Borsook D.

**Specific and somatotopic functional magnetic resonance imaging activation in the trigeminal ganglion by brush and noxious heat.**
Borsook D, DaSilva AF, Ploghaus A, Becerra L.

**Segmentally arranged somatotopy within the face representation of human primary somatosensory cortex.**
Moulton EA, Pendse G, Morris S, Aiello-Lammens M, Becerra L, Borsook D.
*Hum Brain Mapp.* 2009 Mar;30(3):757-65

Anatomical changes at the level of the primary synapse in neuropathic pain: evidence from the spinal trigeminal nucleus.
Wilcox SL, Gustin SM, Macey PM, Peck CC, Murray GM, Henderson LA.

Trigeminal nociceptive transmission in migraineurs predicts migraine attacks.
Stankewitz A, Aderjan D, Eippert F, May A.
*J Neurosci.* 2011 Feb 9;31(6):1937-4011
Reward Circuitry and the Accumbens

**Reward circuitry activation by noxious thermal stimuli.**
Becerra L, Breiter HC, Wise R, Gonzalez RG, Borsook D.

**Corticostratial functional connectivity predicts transition to chronic back pain.**
Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV.

Increased NAc – mPFC Connectivity Predicts Pain Persistence

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Pain Modulation

**Reward circuitry activation by noxious thermal stimuli.**
Becerra L, Breiter HC, Wise R, Gonzalez RG, Borsook D.

**Identification of discrete functional subregions of the human periaqueductal gray.**

**Spinal cord-midbrain functional connectivity is related to perceived pain intensity: a combined spino-cortical FMRI study.**
Sprenger C, Finsterbusch J, Büchel C.

Center for Pain and the Brain, HMS 2015
The habenula and pain: repeated electrical stimulation produces prolonged analgesia but lesions have no effect on formalin pain or morphine analgesia. Cohen SR, Melzack R. Behav Brain Res. 1993 Apr 30;54(2):171-8.


Inter-individual Differences

**Neural correlates of interindividual differences in the subjective experience of pain.**
Coghill RC, McHaffie JG, Yen YF.

**COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor.**

2003

Homozygous for the met158 allele > Pain

**Brain networks predicting placebo analgesia in a clinical trial for chronic back pain.**
Hashmi JA, Baria AT, Baliki MN, Huang L, Schnitzer TJ, Apkarian AV.

2012

Placebo response can be identified a priori
Based on connectivity between PFC and Insula

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Sex Differences

**mu-opioid receptor-mediated antinociceptive responses differ in men and women.**

**Different brain activation patterns to pain and pain-related unpleasantness during the menstrual cycle.**
*Anesthesiology.* 2006 Jul;105(1):120-7

**Greater modulation in Posterior insula and dIPFC.**

**The role of circulating sex hormones in menstrual cycle-dependent modulation of pain-related brain activation.**
Veldhuijzen DS, Keaser ML, Traub DS, Zhuo J, Gullapalli RP, Greenspan JD.

**Are there sex differences in placebo analgesia during visceral pain processing? A fMRI study in healthy subjects.**

**Her versus his migraine: multiple sex differences in brain function and structure.**
Maleki N, Linnman C, Brawn J, Burstein R, Becerra L, Borsook D.

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Pain at the Extremes of Age

**Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease.**

**fMRI reveals neural activity overlap between adult and infant pain.**
Main Pointers: CNS Neurobiology

- Imaging can map specific and functional circuits involved in:
  - Pain Sensation
  - Pain Emotion
  - Pain Modulation
  - Other (specific circuits)

- Imaging can demonstrate individual differences that are present in the response to nociception and pain
  - Sex
  - Age
  - Other (genetic, epigenetic)
Pain Anticipation, Anxiety and Fear

**Dissociating pain from its anticipation in the human brain.**

**Exacerbation of pain by anxiety is associated with activity in a hippocampal network.**

**The responsive amygdala: treatment-induced alterations in functional connectivity in pediatric complex regional pain syndrome.**

2001

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Placebo (Nocebo)

Placebo and opioid analgesia-- imaging a shared neuronal network.
Petrovic P, Kalso E, Petersson KM, Ingvar M. 

Placebo-induced changes in FMRI in the anticipation and experience of pain.
Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. 

Direct evidence for spinal cord involvement in placebo analgesia.
Eippert F, Finsterbusch J, Bingel U, Büchel C. 
Science. 2009 Oct 16;326(5951):404

Activation of the opioidergic descending pain control system underlies placebo analgesia.

Resting state connectivity correlates with drug and placebo response in fibromyalgia patients.
Schmidt-Wilcke T, Ichesco E, Hampson JP, Kairys A, Peltier S, Harte S, Clauw DJ, Harris RE. 

milnacipran

Decreased Fc - anterior cingulate cortex (ACC) and the insular cortex (IC), as well as between the periaqueductal gray (PAG) and the IC

Decreased in activation in thalamus, insula and ACC to placebo and Increased in PFC to anticipation
Pain catastrophizing and neural responses to pain among persons with fibromyalgia.
Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ.
Brain. 2004 Apr;127(Pt 4):835-43.

Cortical responses to pain in healthy individuals depends on pain catastrophizing.
Seminowicz DA, Davis KD.
Empathy and Pain

Empathy for pain involves the affective but not sensory components of pain.
Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD.

Can we share a pain we never felt? Neural correlates of empathy in patients with congenital insensitivity to pain.
Danziger N, Faillenot I, Peyron R.

Oxytocin reduces neural activity in the pain circuitry when seeing pain in others.
Bos PA, Montoya ER, Hermans EJ, Keysers C, van Honk J.
Main Pointers: Applied Biology

• **Imaging Places Placebo in a Neurobiological Context of Systems Neurobiology**
  – Patients may respond differently to Placebo vs. healthy controls
  – Placebo is complex and needs to be understood in terms of long term effects in patients
  – Enhancing and prolonging the Placebo Response is a major challenge

• **Psychological Constructs (e.g., Fear and Catastrophizing) are clear and common elements in the complexity of chronic pain (Altered Brain)**
  – Represent a “brain state” that is fertile for pain chronification
Diseases

- Visceral Pain
- Fibromyalgia
- Chemotherapy Induced Pain
- Small Fiber Neuropathy
- CRPS
- TMJ Pain
- Burning Mouth

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Phantom-Limb Pain

Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation.

Mirror therapy for phantom limb pain: brain changes and the role of body representation.
Foell J, Bekrater-Bodmann R, Diers M, Flor H.

Network-level reorganisation of functional connectivity following arm amputation.
*Neuroimage. 2015 Mar 14.*
Evidence for brain glial activation in chronic pain patients.

Brain plasticity and microglia: is transsynaptic glial activation in the thalamus after limb denervation linked to cortical plasticity and central sensitisation?
Banati RB.
Gray Matter Changes

**Chronic back pain is associated with decreased prefrontal and thalamic gray matter density.**

**Gray matter decrease in patients with chronic tension type headache.**

**Brain gray matter decrease in chronic pain is the consequence and not the cause of pain.**

**Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function.**

**Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain.**
**Other Neuropathic Pain States**

*Altered resting state in diabetic neuropathic pain.*
Cauda F, Sacco K, Duca S, Cocito D, D'Agata F, Geminiani GC, Canavero S.

*Imaging signatures of altered brain responses in small-fiber neuropathy: reduced functional connectivity of the limbic system after peripheral nerve degeneration.*
Hsieh PC, Tseng MT, Chao CC, Lin YH, Tseng WY, Liu KH, Chiang MC, Hsieh ST.
*Pain.* 2015 May; 156(5):904-16.

**Orofacial Neuropathic pain**

*Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes.*
*J Neurosci.* 2011 Apr 20;31(16):5956-64.

**Painful Diabetic Neuropathy**

*fMRI evidence of degeneration-induced neuropathic pain in diabetes: enhanced limbic and striatal activations.*
Tseng MT, Chiang MC, Chao CC, Tseng WY, Hsieh ST.

**Post-herpetic Neuralgia**

Guan M, Ma L, Li L, Yan B, Zhao L, Tong L, Dou S, Xia L, Wang M, Shi D.

**Small Fiber Neuropathy**

*Imaging signatures of altered brain responses in small-fiber neuropathy: reduced functional connectivity of the limbic system after peripheral nerve degeneration.*
Hsieh PC, Tseng MT, Chao CC, Lin YH, Tseng WY, Liu KH, Chiang MC, Hsieh ST.
*Pain.* 2015 May; 156(5):904-16.
**Intrinsic brain networks normalize with treatment in pediatric complex regional pain syndrome.**

Becerra L, Sava S, Simons LE, Drosos AM, Sethna N, Berde C, Lebel AA, Borsook D.


**Rapid treatment-induced brain changes in pediatric CRPS.**


*Brain Struct Funct.* 2014 Dec 17.

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**fMRI reveals distinct CNS processing during symptomatic and recovered complex regional pain syndrome in children.**


*Brain.* 2008 Jul;131(Pt 7):1854-79.
**Psychiatric Disease and Pain**

**Reward-aversion circuitry in analgesia and pain: implications for psychiatric disorders.**
Borsook D, Becerra L, Carlezon WA Jr, Shaw M, Renshaw P, Elman I, Levine J.

**Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain.**
Strigo IA, Simmons AN, Matthews SC, Craig AD, Paulus MP.
*Arch Gen Psychiatry.* 2008 Nov;65(11):1275-84.

**Pain and suicidality: insights from reward and addiction neuroscience.**
Elman I, Borsook D, Volkow ND.
Understanding migraine through the lens of maladaptive stress responses: a model disease of allostatic load.
Borsook D, Maleki N, Becerra L, McEwen B.

The stress model of chronic pain: evidence from basal cortisol and hippocampal structure and function in humans.
Brain. 2013 Mar;136(Pt 3):815-27

Neural circuitry mediating inflammation-induced central pain amplification in human experimental endotoxemia.
Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study.

Excitatory neurotransmitters in brain regions in interictal migraine patients.

Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients.
**Opioids Change the Brain**

**Alterations in brain structure and functional connectivity in prescription opioid-dependent patients.**


**Prescription opioid analgesics rapidly change the human brain.**
Younger JW, Chu LF, D’Arcy NT, Trott KE, Jastrzab LE, Mackey SC.


**Alterations in endogenous opioid functional measures in chronic back pain.**
Martikainen IK, Peciña M, Love TM, Nuechterlein EB, Cummiford CM, Green CR, Harris RE, Stohler CS, Zubieta JK.

*J Neurosci.* 2013 Sep 11;33(37):14729-37

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**DTI**

**Gray Matter**

**Functional Conn.**

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2010 2010

2011 2010 2013

Increased Decreased

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Main Pointers: Chronic Pain

• **Chronic Pain has consequences on our Brains**
  – Disarray of Circuits
  – Disarray of Chemistry
  – Altered Structure (white and gray matter)

• **Imaging has Transformed our understanding of Chronic Pain**
  – Defining an objective measure
  – Transition to Chronic Pain
  – Understanding and Segregating Comorbidity

• **Imaging Transforms the treatment of our patients**
  – Predicting Pain and Treatment
  – Measure pain in the OR
  – Evaluate the long term effects of drugs
CNS activation maps in awake rats exposed to thermal stimuli to the dorsum of the hindpaw.
Becerra L, Chang PC, Bishop J, Borsook D.

MRI structural brain changes associated with sensory and emotional function in a rat model of long-term neuropathic pain.
Seminowicz DA, Laferriere AL, Millecamps M, Yu JS, Coderre TJ, Bushnell MC.

Role of nucleus accumbens in neuropathic pain: linked multi-scale evidence in the rat transitioning to neuropathic pain.
Chang PC, Pollema-Mays SL, Centeno MV, Procissi D, Contini M, Baria AT, Martina M, Apkarian AV.

Metabolic brain activity suggestive of persistent pain in a rat model of neuropathic pain.
Neuroimage. 2014 May 1;91:344-52.
Mechanisms of migraine aura revealed by functional MRI in human visual cortex.
CNS response to a thermal stressor in human volunteers and rats may predict the clinical utility of analgesics

David Borsook¹,²,*, Gautam Pendse¹, Matthew Aiello-Lammens¹, Marcie Glicksman³, Julie Gostic¹, Seth Sherman¹, Joshua Korn¹, Marnie Shaw¹, Ken Stewart¹, Richard Gostic¹, Shelly Bazes¹, Richard Hargreaves⁴ and Lino Becerra¹

Drug Development Research, Feb 2007 23–41,

Parallel buprenorphine phMRI responses in conscious rodents and healthy human subjects.


Analogous responses in the nucleus accumbens and cingulate cortex to pain onset (aversion) and offset (relief) in rats and humans.

Becerra L, Navratilova E, Porreca F, Borsook D.

Drug Development I

**A role for fMRI in optimizing CNS drug development.**
Borsook D, Becerra L, Hargreaves R.
*Nat Rev Drug Discov*. 2006

**Pain facilitation brain regions activated by nalbuphine are revealed by pharmacological fMRI.**

**Decision-making using fMRI in clinical drug development: revisiting NK-1 receptor antagonists for pain.**

**Modulation of CNS pain circuitry by intravenous and sublingual doses of buprenorphine.**
Use of functional imaging across clinical phases in CNS drug development.
Borsook D, Becerra L, Fava M.

Learning to identify CNS drug action and efficacy using multistudy fMRI data.
Sci Transl Med. 2015 Feb 11;7(274):274ra16

Pharmacologic modulation of hand pain in osteoarthritis: a double-blind placebo-controlled functional magnetic resonance imaging study using naproxen.
Arthritis Rheumatol. 2015 Mar;67(3):741-51

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Main Pointers: Translational Aspects

• Imaging is a “language of translation”
  – Better animal models based on circuits
• Imaging can improve Drug Development
  – Go-no go decisions
  – Surrogate models
  – Functional Circuits = Behaviors
• Imaging can Improve Clinical Trials
  – Go-nogo decisions in Phase I
  – Responders vs. Non-responders in Phase II
  – Long term effects (e.g., disease modification)
Clinical Presentation

Psychophysics

Resting State Networks

Borsook et al., 2008
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- R01 NS075018 (DB)
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Dr. Apkarian has studied pain for two decades, both in animal models and fMRI studies in humans. His current interests include cortical dynamics of pain as well as brain plasticity. His overall goal is the uncovering of brain mechanisms underlying PAIN QUALIA. This work aims to alleviate clinical pain conditions and achieve a more profound theoretical and mechanistic understanding of the brain.

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>144 Peer Reviewed Papers

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