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

David Borsook MD PhD
Professor, Harvard Medical School
Director, Center for Pain and the Brain

Wall and Melzack

19 November 1965, Volume 150, Number 3699 SCIENCE

Pain Mechanisms: A New Theory

A gate control system modulates sensory input from the skin before it evokes pain perception and response.

Ronald Melzack and Patrick D. Wall

The nature of pain has been the subject of bitter controversy since the turn of the century (*1*). There are currently two opposing theories of pain: (i) specificity theory, which holds that pain is a specific modality like vision or hearing, "with its own central and peripheral apparatus" (*2*), and (ii) pattern theory, which maintains that the nerve impulse pattern for pain is produced by intense stimulation of nonspecific receptors since "there are no specific fibers and no specific endings" (*3*). Both theories derive from earlier concepts proposed by von Frey (*4*) and Goldscheider (*5*) in 1894, and historically they are held to be mutually exclusive. Since it is our purpose here to propose a new theory of pain mechanisms, we shall state explicitly at the outset where we agree and disagree with specificity and pattern theories.

Specificity Theory

Specificity theory proposes that a mosaic of specific pain receptors in body tissue projects to a pain center in the brain. It maintains that free nerve endings are pain receptors (*4*) and generate pain impulses that are carried by A-delta and C fibers in peripheral nerves (*6*) and by the lateral spinothalamic tract in the spinal cord (*2*) to a pain center in the thalamus (*7*). Despite its apparent simplicity, the theory contains an explicit statement of physiological specialization and an implicit psychological assumption (*8, 9*). Consider the proposition that the skin contains "pain receptors." To say that a receptor responds only to intense, noxious stimulation of the skin is a physiological statement of fact; it says that the receptor is specialized to respond to a particular kind of stimulus. To call a receptor a "pain receptor," however, is a psychological assumption: it implies a direct connection from the receptor to a brain center where pain is felt (Fig. 1), so that stimulation of the receptor must always elicit pain and only the sensation of pain. This distinction between physiological specialization and psychological assumption also applies to peripheral fibers and central projection systems (*9*).

The facts of physiological specialization provide the power of specificity theory. Its psychological assumption is its weakness. As in all psychological theories, there is implicit in specificity theory the conception of a nervous system; and the model is that of a fixed, direct-line communication system from the skin to the brain. This facet of specificity theory, which imputes a direct, invariant relationship between stimulus and sensation, is examined here in the light of the clinical, psychological, and physiological evidence concerning pain.

Clinical evidence. The pathological pain states of causalgia (a severe burning pain that may result from a partial lesion of a peripheral nerve), phantom limb pain (which may occur after amputation of a limb), and the peripheral neuralgias (which may occur after peripheral nerve infections or degenerative diseases) provide a dramatic refutation of the concept of a fixed, direct-line nervous system. Four features of these syndromes plague patient, physician, and theorist (*8, 10*).

1) Surgical lesions of the peripheral and central nervous system have been singularly unsuccessful in abolishing these pains permanently, although the lesions have been made at almost every level (Fig. 2). Even after such operations, pain can often still be elicited by stimulation below the level of section and may be more severe than before the operation (*8, 10*).

2) Gentle touch, vibration, and other nonnoxious stimuli (*8, 10*) can trigger excruciating pain, and sometimes pain occurs spontaneously for long periods without any apparent stimulus. The fact that the thresholds to these stimuli are raised rather than lowered in causalgia and the neuralgias (*10*), together with the fact that referred pain can often be triggered by mild stimulation of normal skin (*8*), makes it unlikely that the pains can be explained by postulating pathologically hypersensitive "pain receptors."

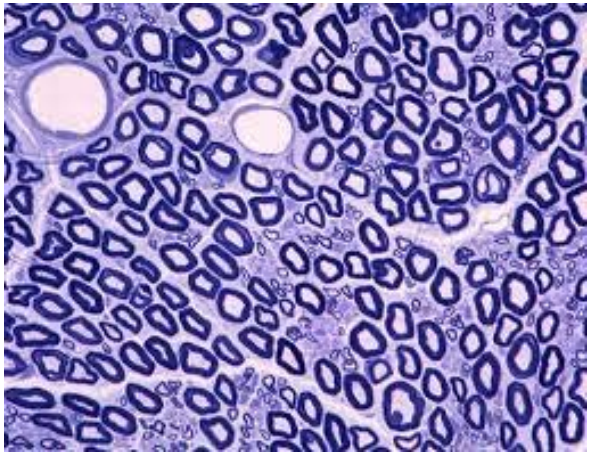
3) The pains and new "trigger zones" may spread unpredictably to unrelated parts of the body where no pathology exists (*8, 11*).

4) Pain from hyperalgesic skin areas often occurs after long delays, and continues long after removal of the stimulus (*10*). Gentle rubbing, repeated pin pricks, or the application of a warm test tube may produce sudden, severe pain after delays as long as 35 seconds. Such delays cannot be attributed simply to conduction in slowly conducting fibers; rather, they imply a remarkable temporal and spatial summation of inputs in the production of these pain states (*8, 10*).

Psychological evidence. The psychological evidence fails to support the assumption of a one-to-one relation-

Dr. Melzack is associate professor in the department of psychology at McGill University, Montreal, Canada. Dr. Wall is professor in the department of biology at the Massachusetts Institute of Technology, Cambridge.

"Similarly there is evidence that central nervous system pathways have specialized functions that play a role in pain mechanisms"

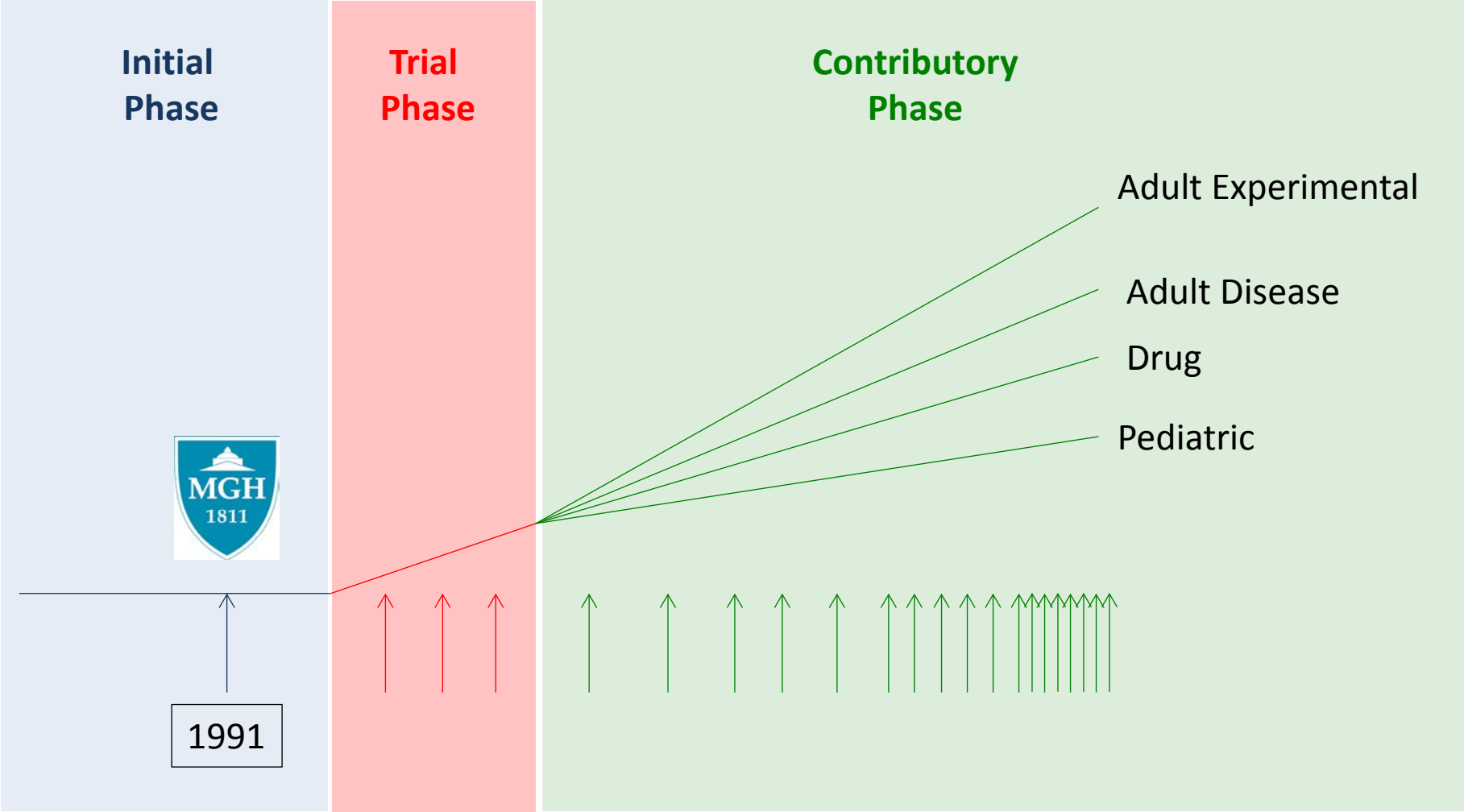


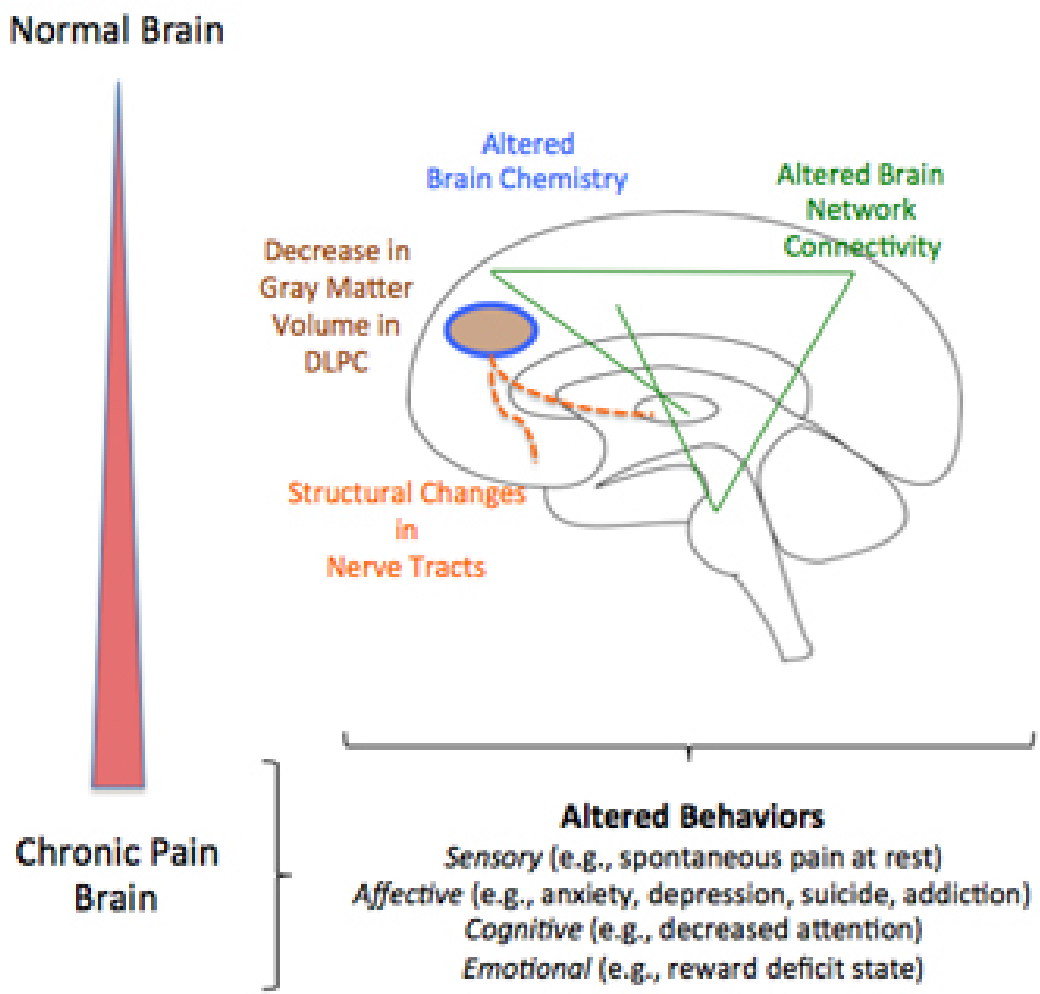
neuropathology-web.org

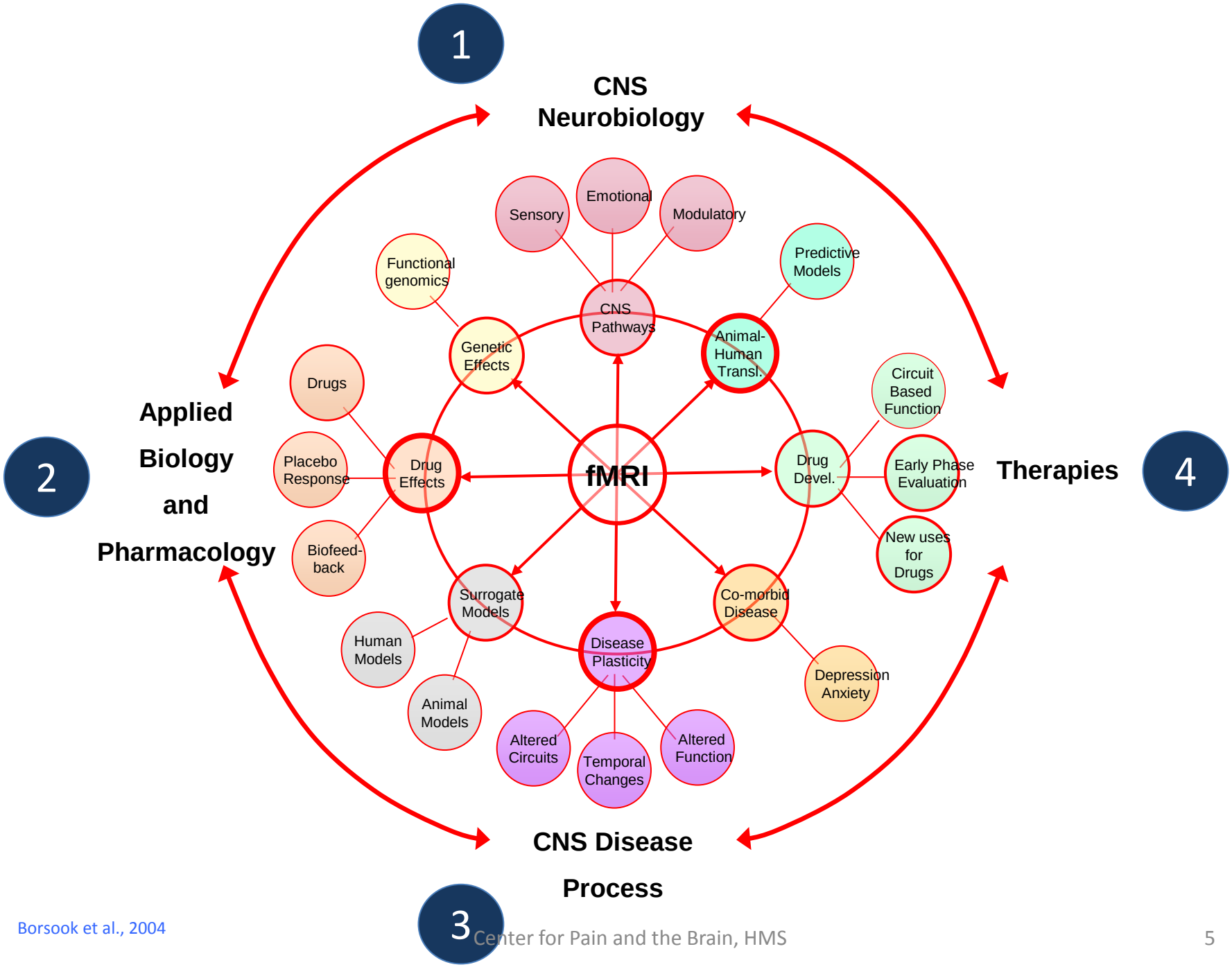
gamerssphere.com

Imaging Pain In North America

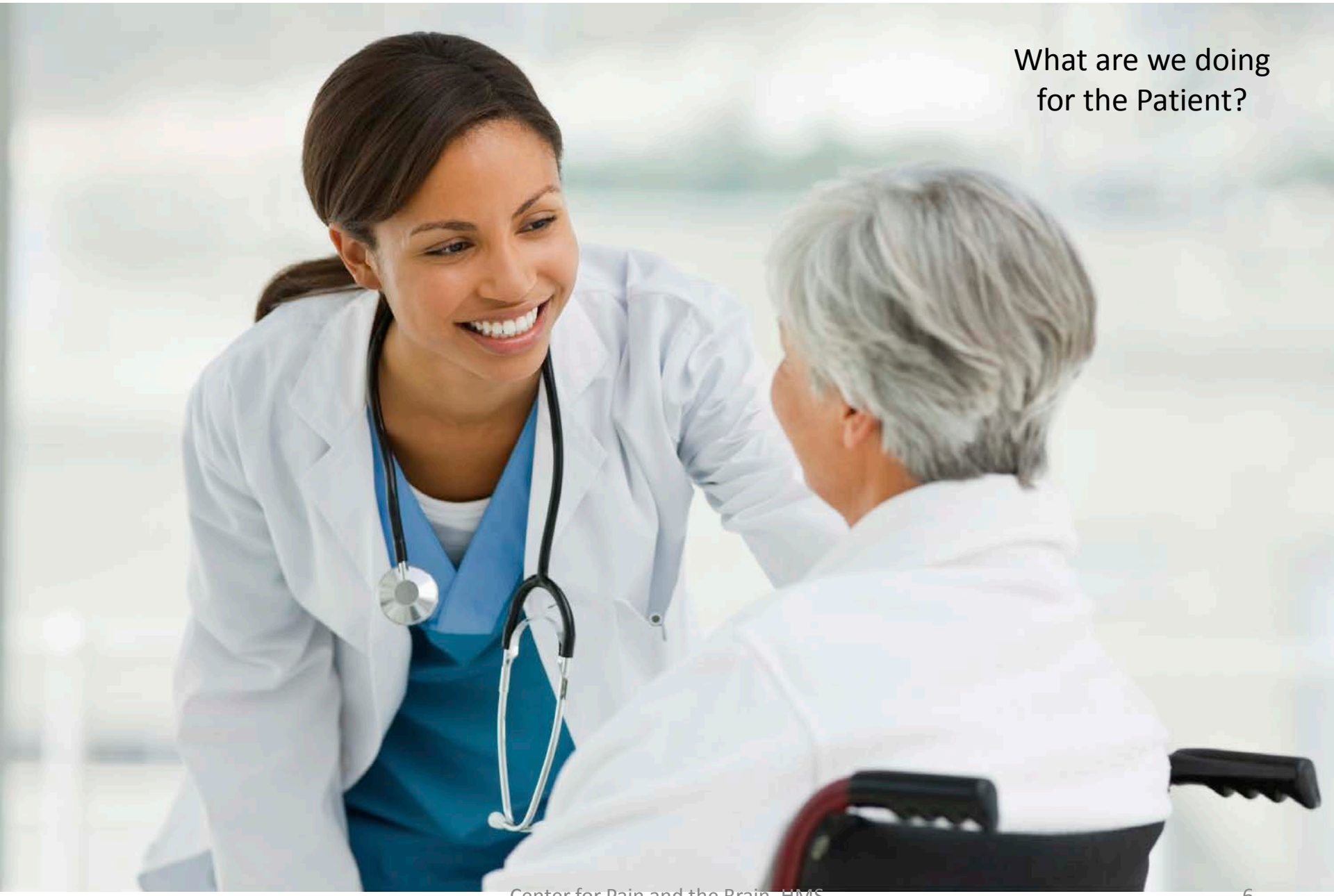
Atlas, Baliki, Bajic, Younger, DaSilva, Hubbard, Linnman, Loggia, Simons, and Many Others


Initial Phase
Trial Phase
Contributory Phase
Adult Experimental
Adult Disease
Drug
Pediatric
MGH
1811
1991


Normal Brain
Altered
Brain Chemistry
Altered Brain
Network
Connectivity
Decrease in
Gray Matter
Volume in
DLPC
Structural Changes
in
Nerve Tracts
Chronic Pain
Brain
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)

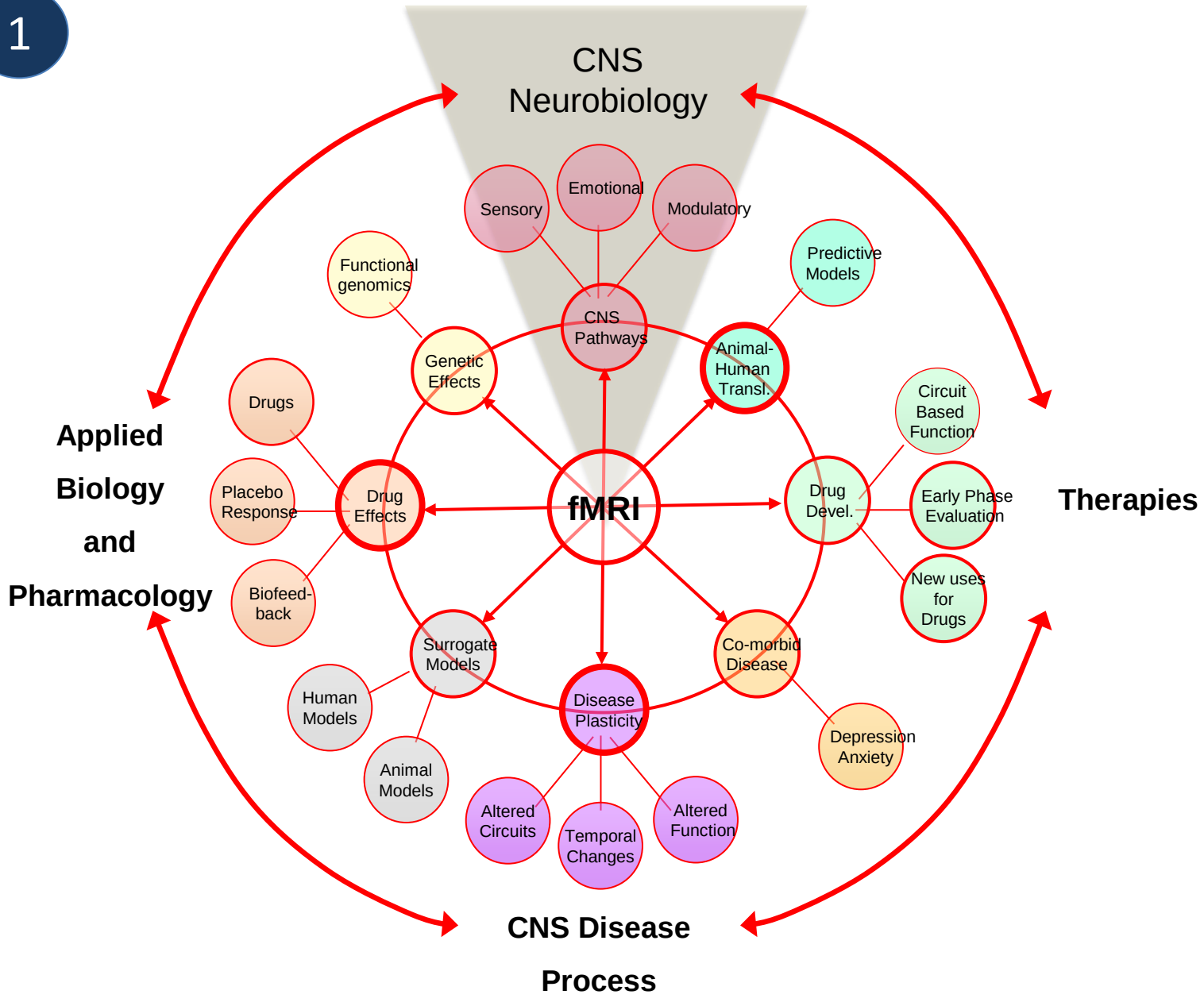


Borsook et al., 2004



What are we doing for the Patient?

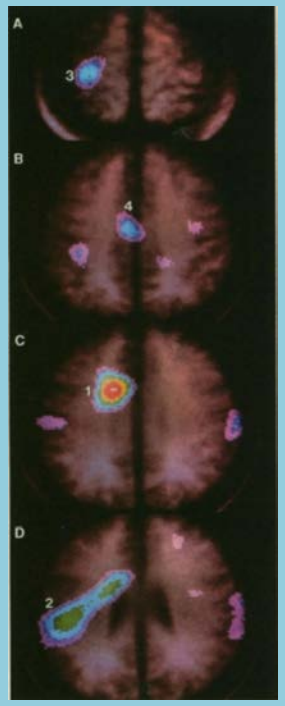
1


CNS
Neurobiology
Sensory
Emotional
Modulatory
Functional genomics
Predictive Models
CNS Pathways
Genetic Effects
Animal-Human Transl.
Drugs
Circuit Based Function
Applied Biology and Pharmacology
Placebo Response
Drug Effects
fMRI
Drug Devel.
Early Phase Evaluation
Therapies
Biofeed-back
New uses for Drugs
Surrogate Models
Co-morbid Disease
Human Models
Disease Plasticity
Depression Anxiety
Animal Models
Altered Circuits
Temporal Changes
Altered Function
CNS Disease Process

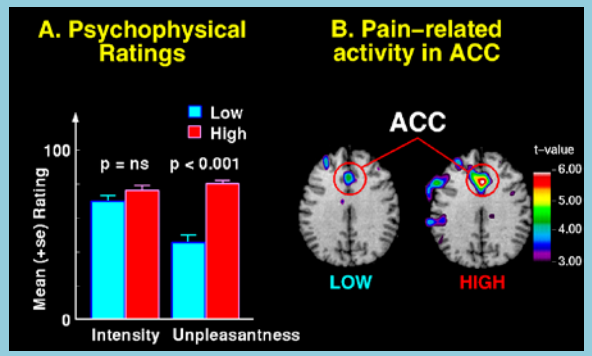
Sensory and Affective Components Of Pain

Multiple representations of pain in human cerebral cortex.
Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH.
Science. 1991 Mar 15;251(4999):1355-8.

Pain affect encoded in human anterior cingulate but not somatosensory cortex.
Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC.
Science. 1997 Aug 15;277(5328):968-71.

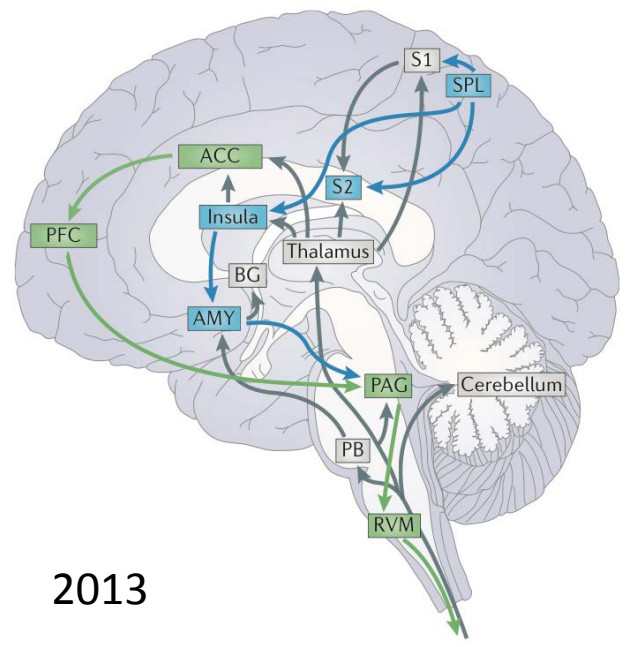


1991



1997

Cognitive and emotional control of pain and its disruption in chronic pain.
Bushnell MC, Ceko M, Low LA.
Nat Rev Neurosci. 2013 Jul;14(7):502-11.



2013

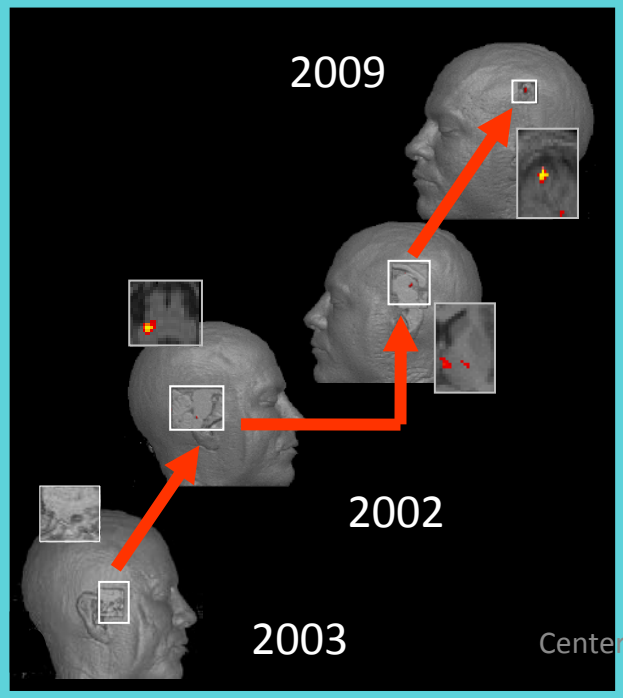
Attentional and emotional factors modulate pain perception via different pathways

Mapping a Sensory Pathway

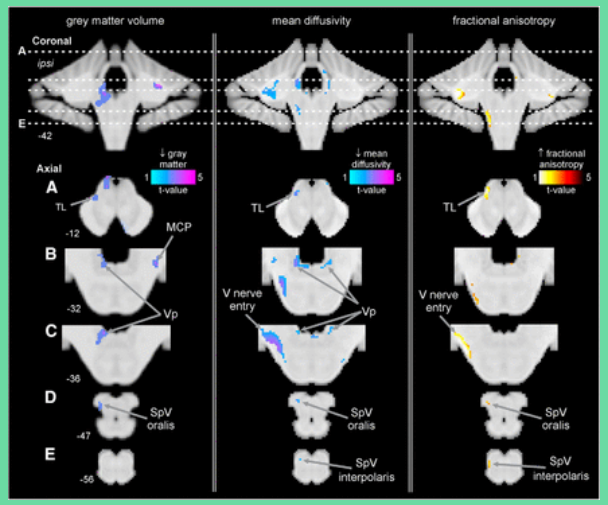
Somatotopic activation in the human trigeminal pain pathway.
DaSilva AF, Becerra L, Makris N, Strassman AM, Gonzalez RG, Geatrakis N, Borsook D.
J Neurosci. 2002 Sep 15;22(18):8183-92.

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.
J Neurosci. 2003 Aug 27;23(21):7897-903.2002

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

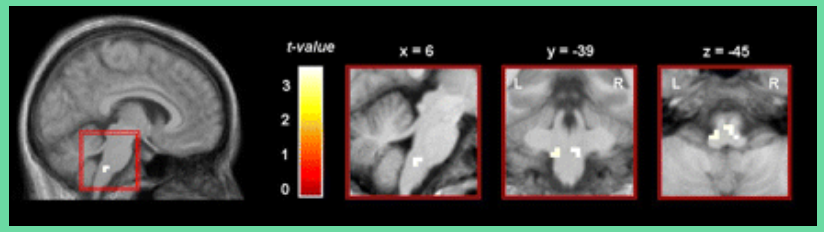


Anatomical changes at the level of the primary synapse in neuropathic pain: evidence from the spinal trigeminal nucleus.
Wilcox SL, Gustin SM, Macey PM, Peck CC, Murray GM, Henderson LA.
J Neurosci. 2015 Feb 11;35(6):2508-15.



2015

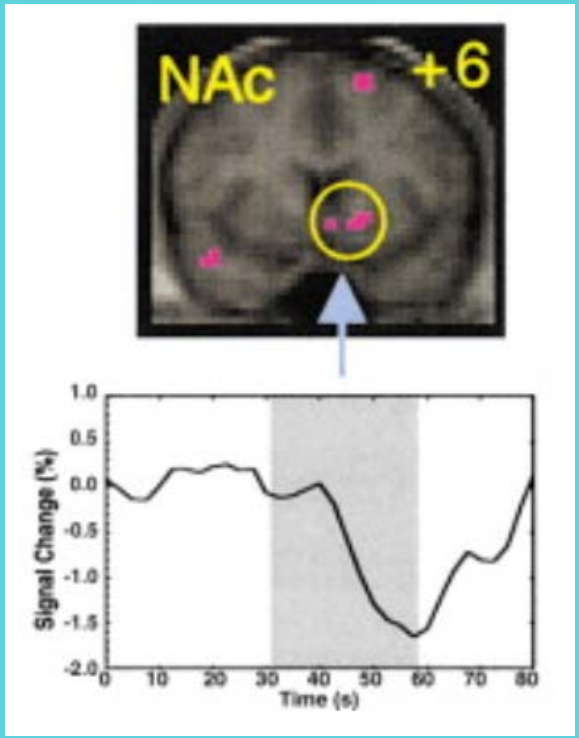
Trigeminal nociceptive transmission in migraineurs predicts migraine attacks.
Stankewitz A, Aderjan D, Eippert F, May A.
J Neurosci. 2011 Feb 9;31(6):1937-43011



2011

Reward Circuitry and the Accumbens

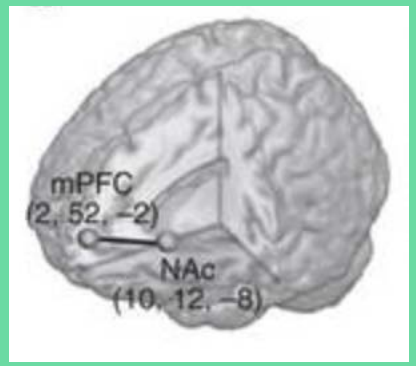
Reward circuitry activation by noxious thermal stimuli.
Becerra L, Breiter HC, Wise R, Gonzalez RG, Borsook D.
Neuron. 2001 Dec 6;32(5):927-46



2001

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

Nat Neurosci. 2012 Jul 1;15(8):1117-9.

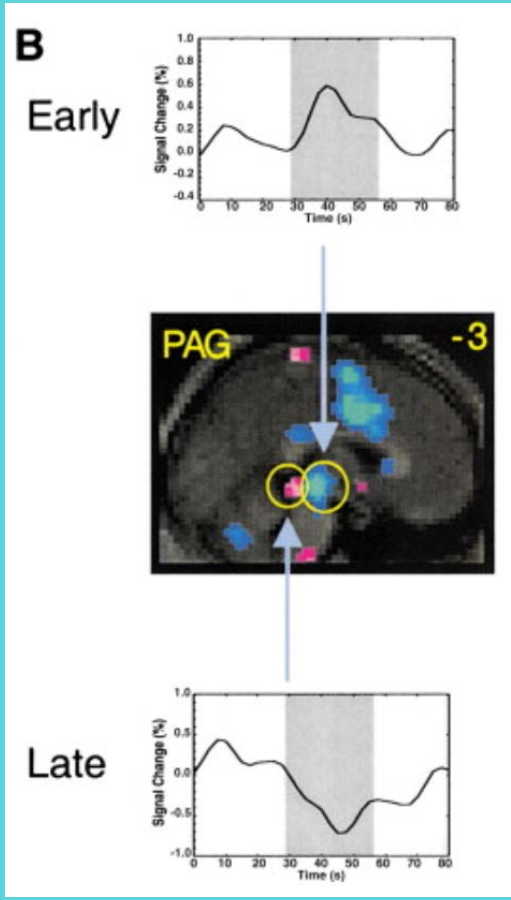


2012

Increased NAc – mPFC Connectivity
Predicts Pain Persistence

Pain Modulation

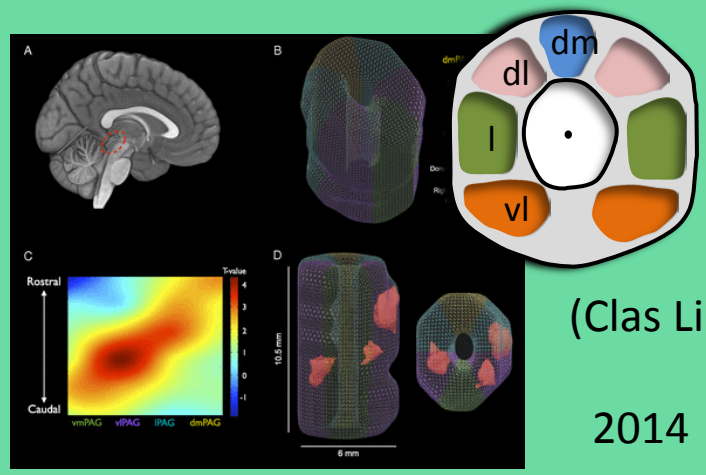
Reward circuitry activation by noxious thermal stimuli.
Becerra L, Breiter HC, Wise R, Gonzalez RG, Borsook D.
Neuron. 2001 Dec 6;32(5):927-46



2001

Identification of discrete functional subregions of the human periaqueductal gray.
Satpute AB, Wager TD, Cohen-Adad J, Bianciardi M, Choi JK, Buhle JT, Wald LL, Barrett LF.
Proc Natl Acad Sci U S A. 2013 Oct 15;110(42):17101-6.

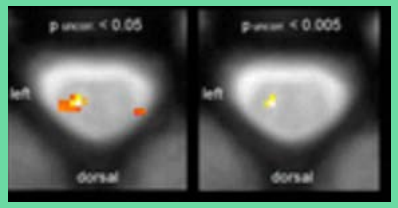
High Field (7T)

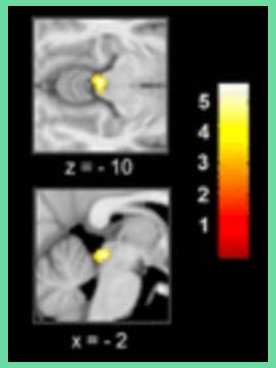


(Clas Linnman)

2014

Spinal cord-midbrain functional connectivity is related to perceived pain intensity: a combined spino-cortical FMRI study.
Sprenger C, Finsterbusch J, Büchel C.
J Neurosci. 2015 Mar 11;35(10):4248-57.



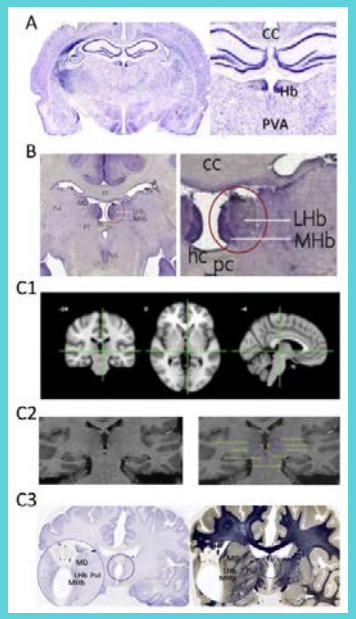


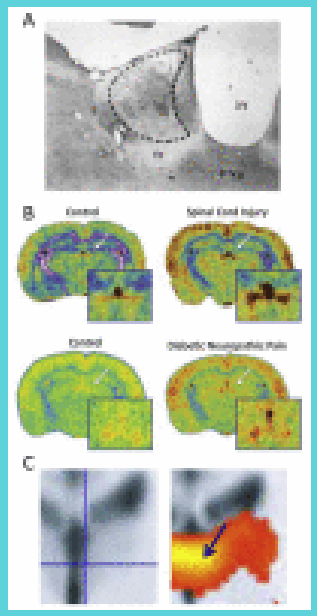
2015

Dissecting Circuits

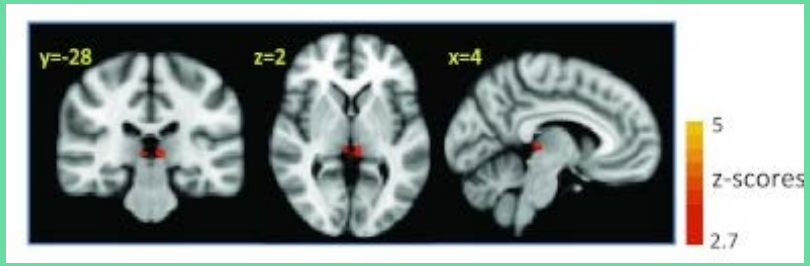
The **habenula** and pain: repeated electrical stimulation produces prolonged analgesia but lesions have no effect on formalin pain or morphine analgesia.
Cohen SR, Melzack R.
Behav Brain Res. 1993 Apr 30;54(2):171-8.

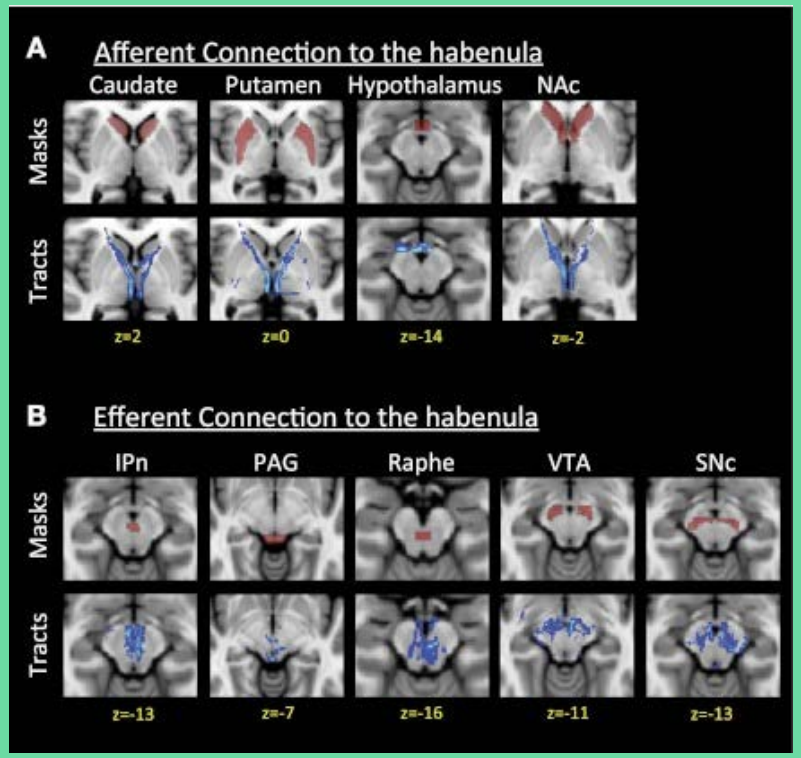
Unmasking the mysteries of the **habenula** in pain and analgesia.
Shelton L, Becerra L, Borsook D.
Prog Neurobiol. 2012 Feb;96(2):208-19





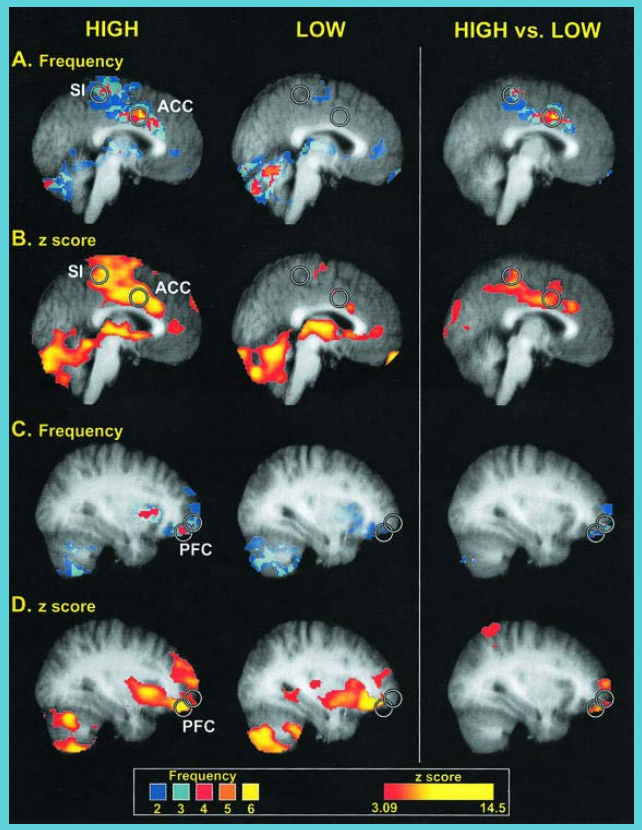
Mapping pain activation and connectivity of the human habenula.
Shelton L, Pendse G, Maleki N, Moulton EA, Lebel A, Becerra L, Borsook D.
J Neurophysiol. 2012 May;107(10):2633-48.





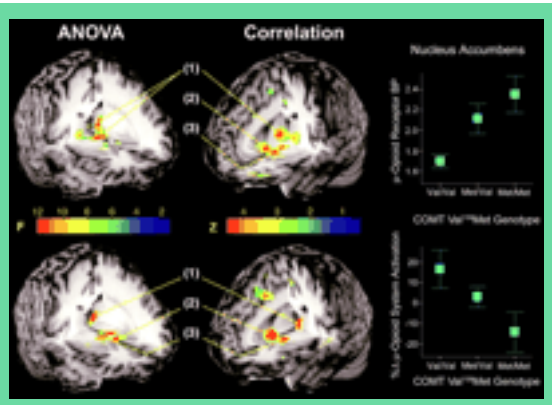
Inter-individual Differences

Neural correlates of interindividual differences in the subjective experience of pain.
Coghill RC, McHaffie JG, Yen YF.
Proc Natl Acad Sci U S A. 2003 Jul 8;100(14):8538-42.



2003

COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor.
Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D.
Science. 2003 Feb 21;299(5610):1240-3.



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.
Pain. 2012 Dec;153(12):2393-402.

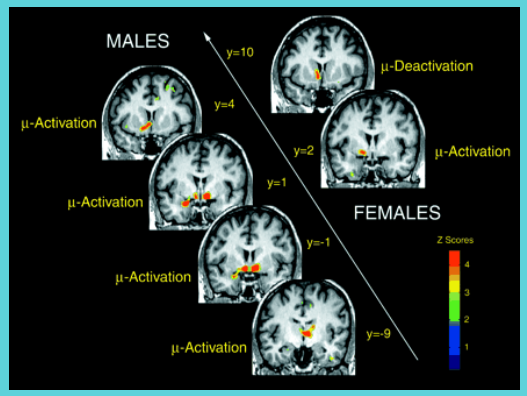
2012

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

Sex Differences

mu-opioid receptor-mediated antinociceptive responses differ in men and women.
Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, Meyer CR, Koeppe RA, Stohler CS.
J Neurosci. 2002 Jun 15;22(12):5100-7.

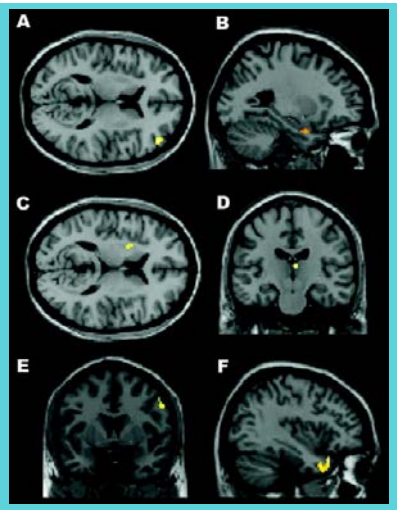
Men > Women in anterior thalamus, ventral basal ganglia, and amygdala



2002

Different brain activation patterns to pain and pain-related unpleasantness during the menstrual cycle.
Choi JC, Park SK, Kim YH, Shin YW, Kwon JS, Kim JS, Kim JW, Kim SY, Lee SG, Lee MS.
Anesthesiology. 2006 Jul;105(1):120-7

Luteal . Follicular

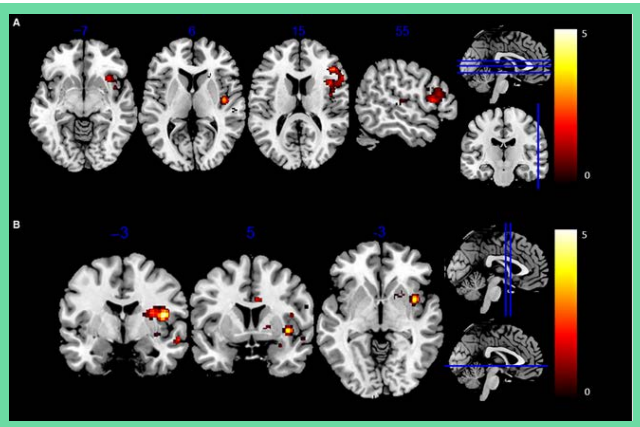


2006

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.
Pain. 2013 Apr;154(4):548-59. doi: 10.1016/j.**pain**.2012.12.019.

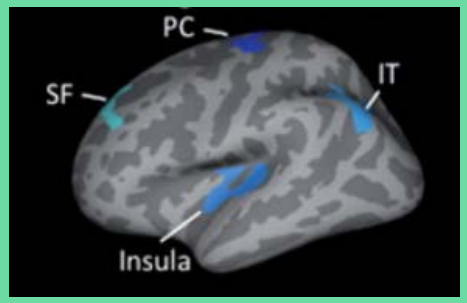
Are there sex differences in placebo analgesia during visceral pain processing? A fMRI study in healthy subjects.
Theysohn N, Schmid J, Icenhour A, Mewes C, Forsting M, Gizewski ER, Schedlowski M, Elsenbruch S, Benson S.
Neurogastroenterol Motil. 2014 Dec;26(12):1743-53. d

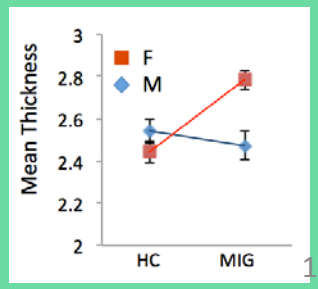
Greater modulation in Posterior insula and dlPFC



2014

Her versus his migraine: multiple sex differences in brain function and structure.
Maleki N, Linnman C, Brawn J, Burstein R, Becerra L, Borsook D.
Brain. 2012 Aug;135(Pt 8):2546-59.



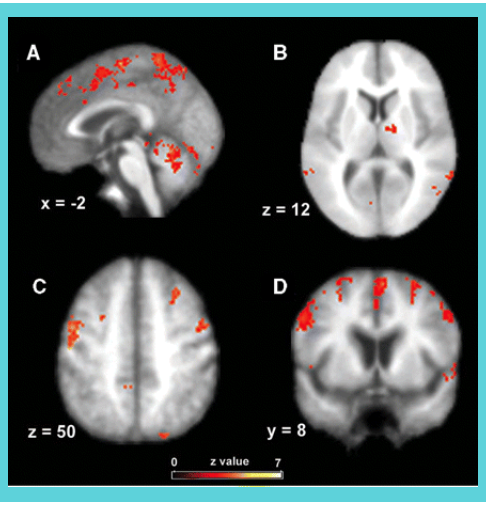


2012

Pain at the Extremes of Age

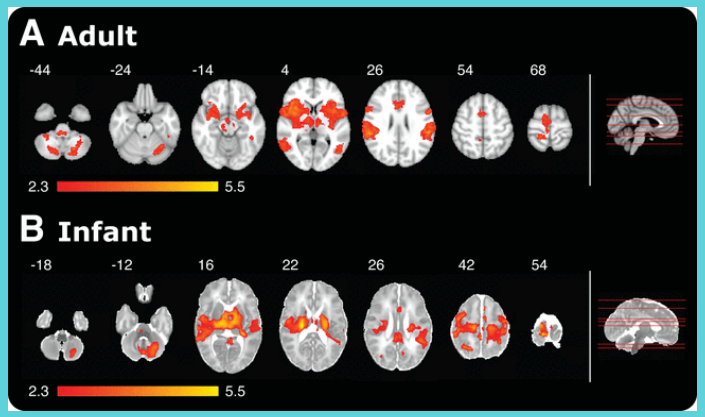
Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease.
Cole LJ, Farrell MJ, Duff EP, Barber JB, Egan GF, Gibson SJ.
Brain. 2006 Nov;129(Pt 11):2957-65.

not in the infant amygdala or orbitofrontal cortex

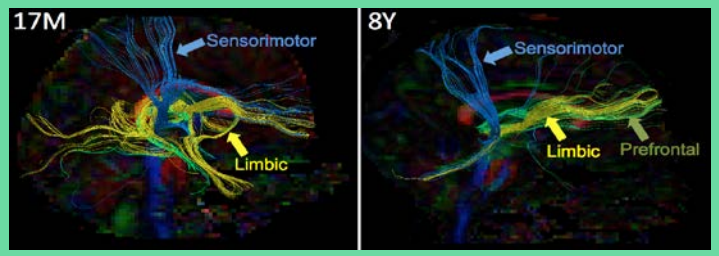


2006

fMRI reveals neural activity overlap between adult and infant pain.
Goksan S, Hartley C, Emery F, Cockrill N, Poorun R, Moultrie F, Rogers R, Campbell J, Sanders M, Adams E, Clare S, Jenkinson M, Tracey I, Slater R.
Elife. 2015 Apr 21;4.



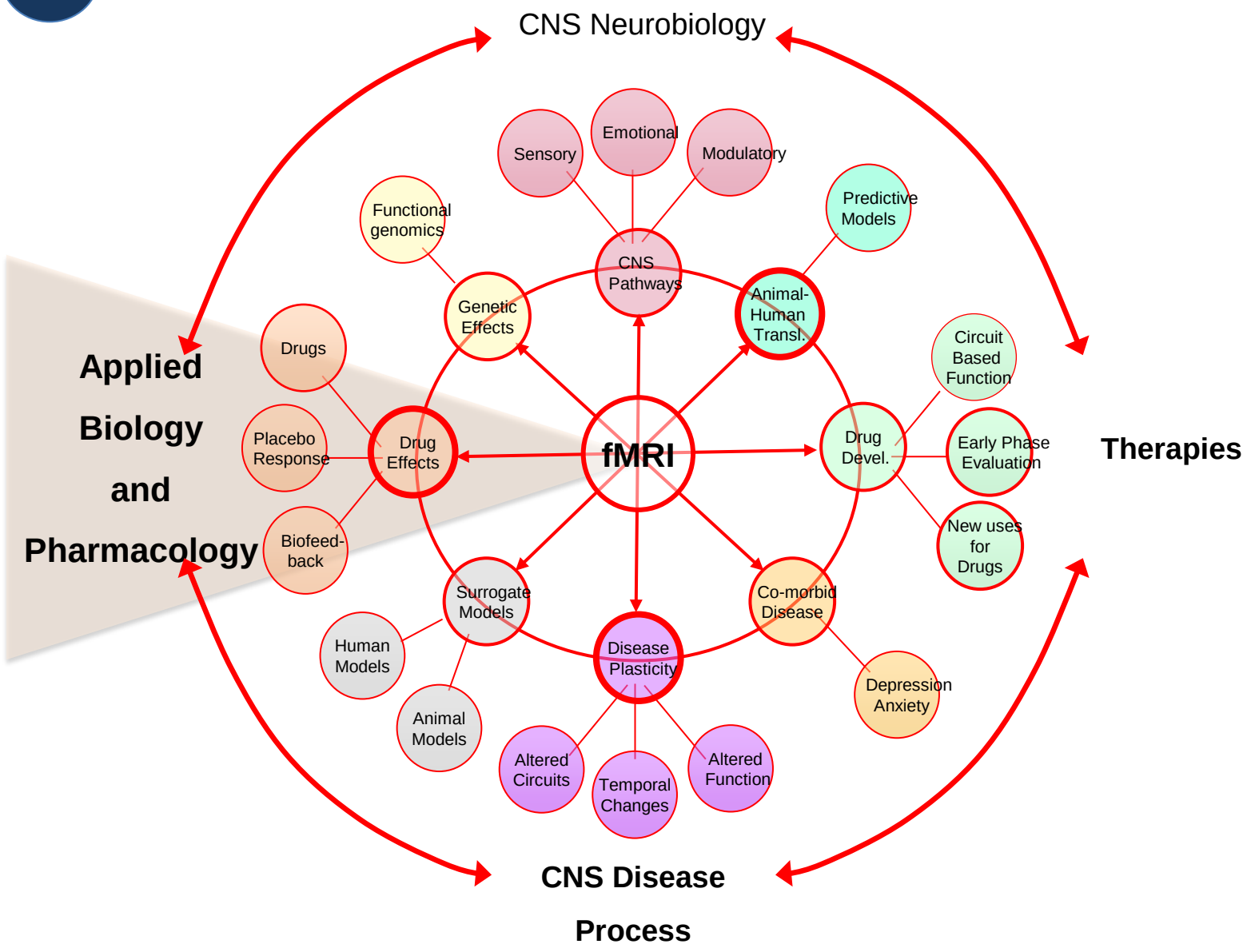
2015



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)

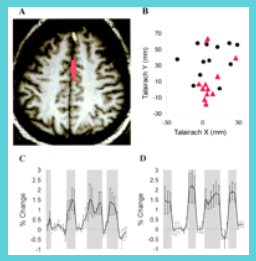
2


CNS Neurobiology
Sensory
Emotional
Modulatory
Functional genomics
Predictive Models
CNS Pathways
Genetic Effects
Animal-Human Transl.
Drugs
Circuit Based Function
Applied Biology and Pharmacology
Placebo Response
Drug Effects
fMRI
Drug Devel.
Early Phase Evaluation
Therapies
Biofeed-back
New uses for Drugs
Surrogate Models
Co-morbid Disease
Human Models
Disease Plasticity
Depression Anxiety
Animal Models
Altered Circuits
Temporal Changes
Altered Function
CNS Disease Process

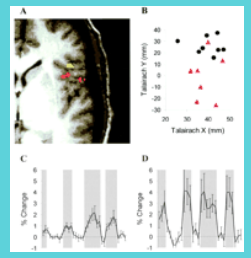
Pain Anticipation, Anxiety and Fear

Dissociating pain from its anticipation in the human brain.
Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, Rawlins JN.
Science. 1999 Jun 18;284(5422):1979-81.

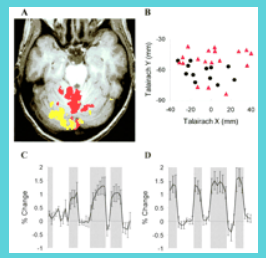
ACC



A-Insula

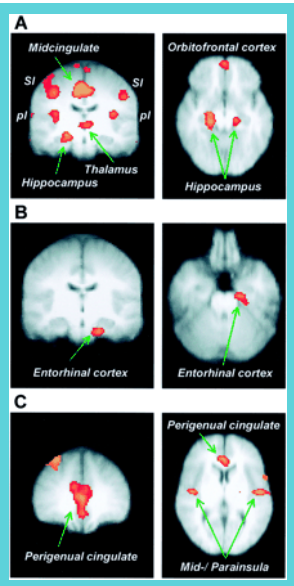


Cerebellum



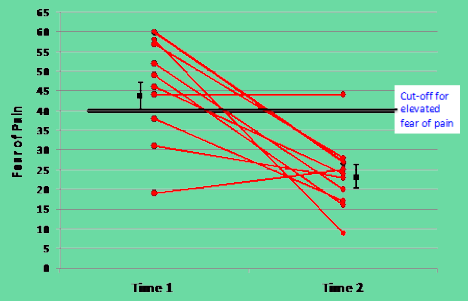
1999

Exacerbation of pain by anxiety is associated with activity in a hippocampal network.
Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JN, Tracey I.
J Neurosci. 2001 Dec 15;21(24):9896-903.

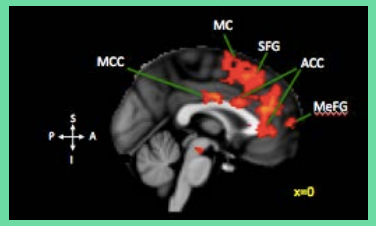


2001

The responsive amygdala: treatment-induced alterations in functional connectivity in pediatric complex regional pain syndrome.
Simons LE, Pielech M, Erpelding N, Linnman C, Moulton E, Sava S, Lebel A, Serrano P, Sethna N, Berde C, Becerra L, Borsook D.
Pain. 2014 Sep;155(9):1727-42.



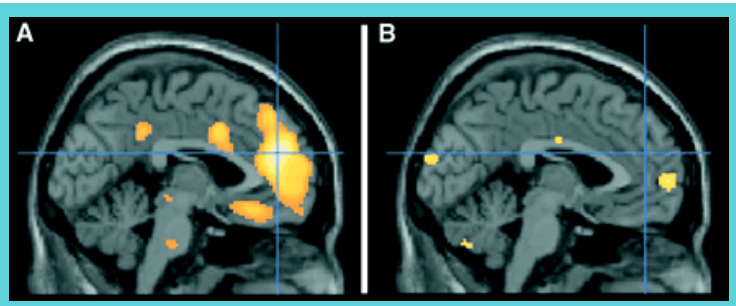
Rx resp. and Δ Pain related Fear



2014

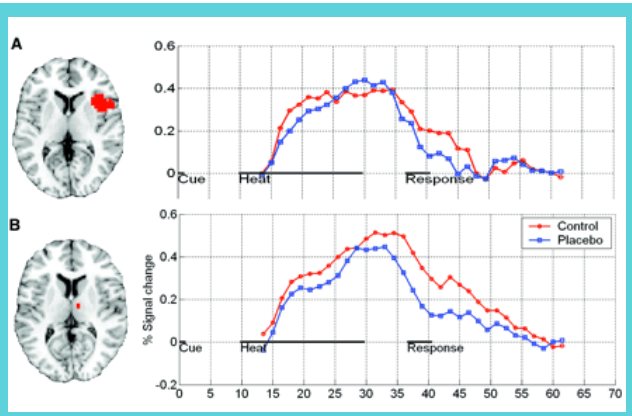
Placebo (Nocebo)

Placebo and opioid analgesia-- imaging a shared neuronal network.
Petrovic P, Kalso E, Petersson KM, Ingvar M.
Science. 2002 Mar 1;295(5560):1737-40.



2002

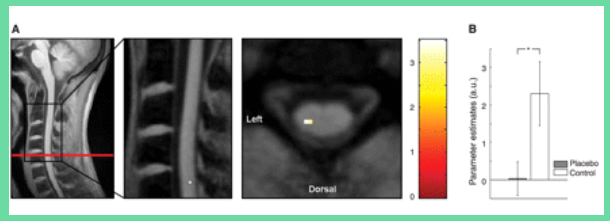
Placebo-induced changes in FMRI in the anticipation and experience of pain.
Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD.
Science. 2004 Feb 20;303(5661):1162-7.



2004

Decreased in activation in thalamus, insula and ACC to placebo and Increased in PFC to anticipation

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



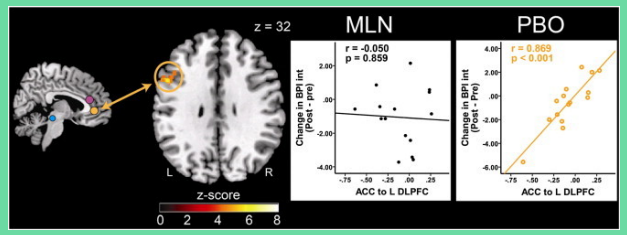
2009

Activation of the opioidergic descending pain control system underlies placebo analgesia.
Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, Büchel C.
Neuron. 2009 Aug 27;63(4):533-43.

milnacipran

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.
Neuroimage Clin. 2014 Sep 16;6:252-61.

milnacipran



2014

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

Pain Catastophizing

www.pinterest.com

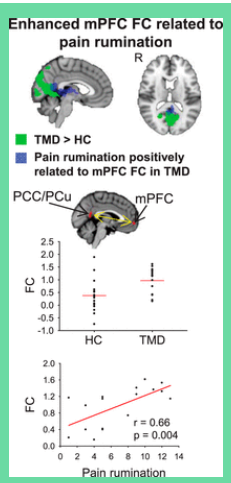
Pain catastrophizing and neural responses to pain among persons with fibromyalgia.
Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ.
Brain. 2004 Apr;127(Pt 4):835-43.

2004

Cortical responses to pain in healthy individuals depends on pain catastrophizing.
Seminowicz DA, Davis KD.
Pain. 2006 Feb;120(3):297-306.

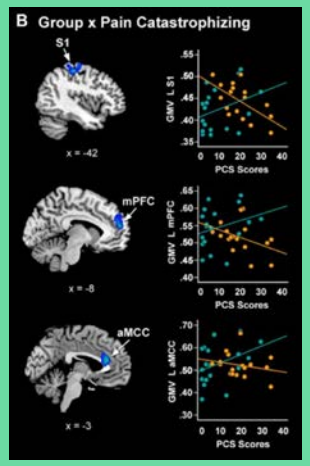
2006

Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination.
Kucyi A, Moayedi M, Weissman-Fogel I, Goldberg MB, Freeman BV, Tenenbaum HC, Davis KD.
J Neurosci. 2014 Mar 12;34(11):3969-75.



2014

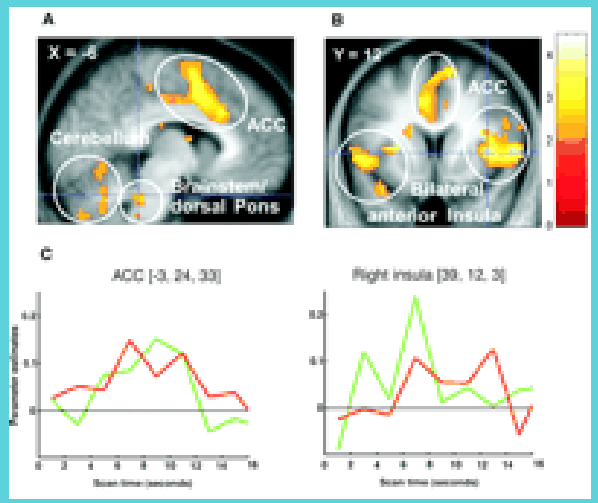
Altered Brain Structure and Function Correlate with Disease Severity and Pain Catastrophizing in Migraine Patients.
Hubbard CS, Khan SA, Keaser ML, Mathur VA, Goyal M, Seminowicz DA.
Eneuro. 2014 Dec 30;1(1):e20.14.



2015

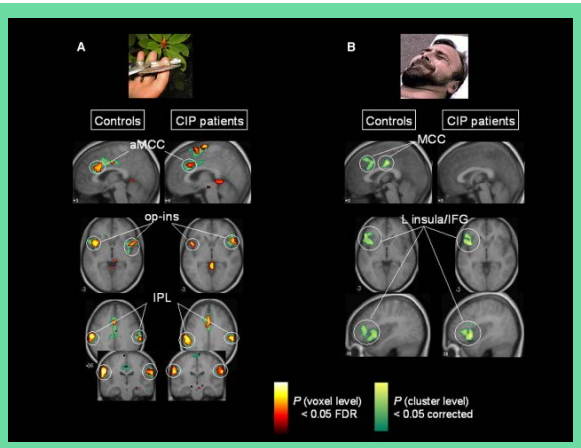
Empathy and Pain

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.
Science. 2004 Feb 20;303(5661):1157-62.



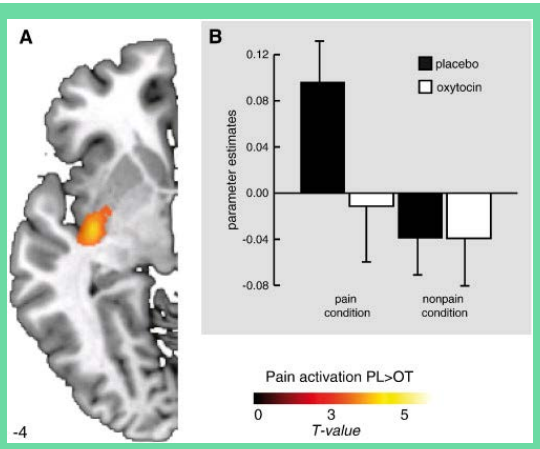
2004

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.
Neuron. 2009 Jan 29;61(2):203-12.



2009

Oxytocin reduces neural activity in the pain circuitry when seeing pain in others.
Bos PA, Montoya ER, Hermans EJ, Keysers C, van Honk J.
Neuroimage. 2015 Jun;113:217-24.



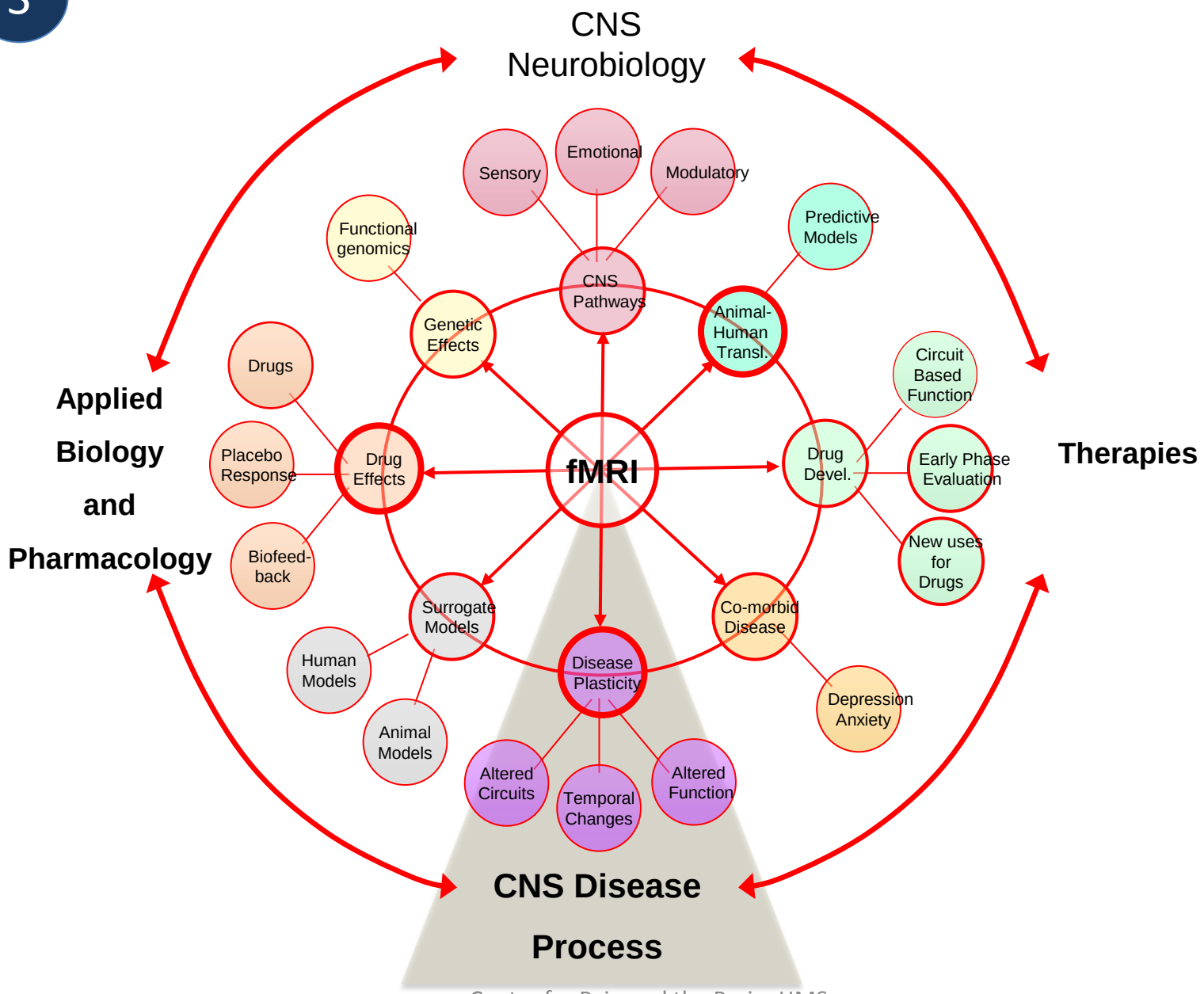
2015

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

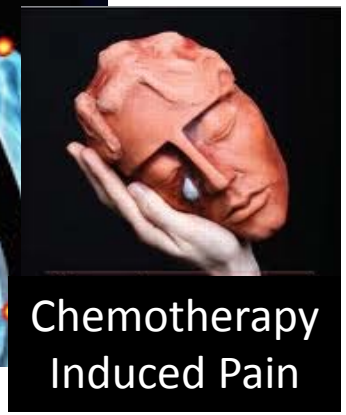
- Psychological Constructs (e.g., Fear and Catastrophizing) are clear and common elements in the complexity of chronic pain (Altered Brain)
  - Represent a “brain state” that is fertile for pain chronification

3


CNS
Neurobiology
Sensory
Emotional
Modulatory
Functional genomics
Predictive Models
CNS Pathways
Genetic Effects
Animal-Human Transl.
Drugs
Circuit Based Function
Applied Biology and Pharmacology
Placebo Response
Drug Effects
fMRI
Drug Devel.
Early Phase Evaluation
Therapies
Biofeed-back
New uses for Drugs
Surrogate Models
Co-morbid Disease
Human Models
Disease Plasticity
Depression Anxiety
Animal Models
Altered Circuits
Temporal Changes
Altered Function
CNS Disease Process

Diseases

www.touchmatters.ca

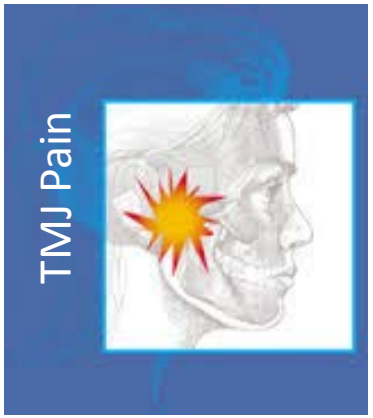


www.crcpress.com

www.vereencenter.com

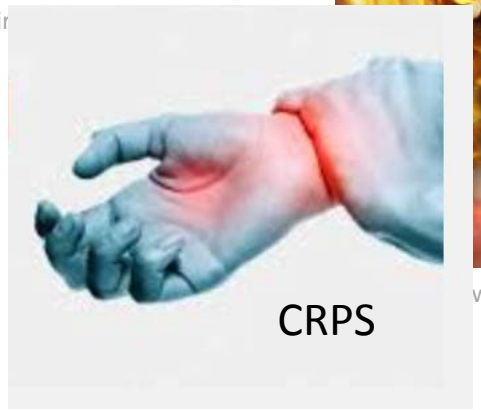
edmontonchir

wdvoice.com



www.nidcr.nih.gov

www.newworldliteracy.com

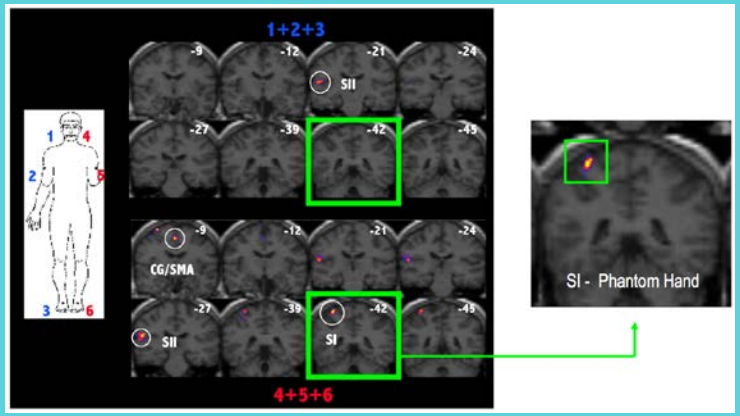


painhealth.csse.uwa.edu.au

Phantom Limb Pain

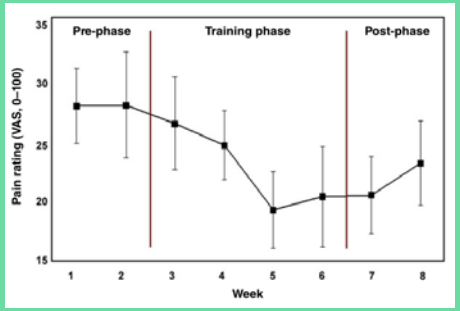
Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation.
Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E.
Nature. **1995** Jun 8;375(6531):482-4.

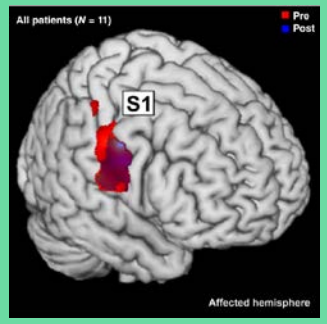
1995



1999

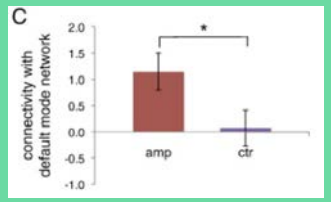
Mirror therapy for phantom limb pain: brain changes and the role of body representation.
Foell J, Bekrater-Bodmann R, Diers M, Flor H.
Eur J Pain. 2014 May;18(5):729-39.

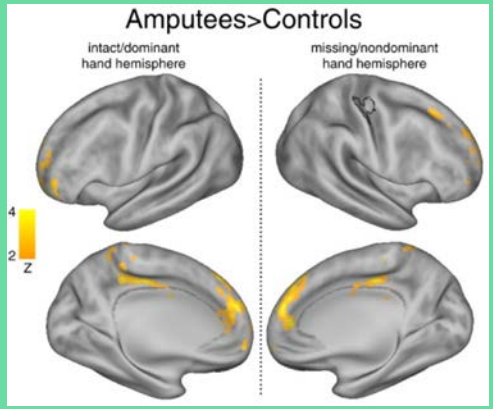




2013

Network-level reorganisation of functional connectivity following arm amputation.
Makin TR, Filippini N, Duff EP, Henderson Slater D, Tracey I, Johansen-Berg H.
Neuroimage. 2015 Mar 14.





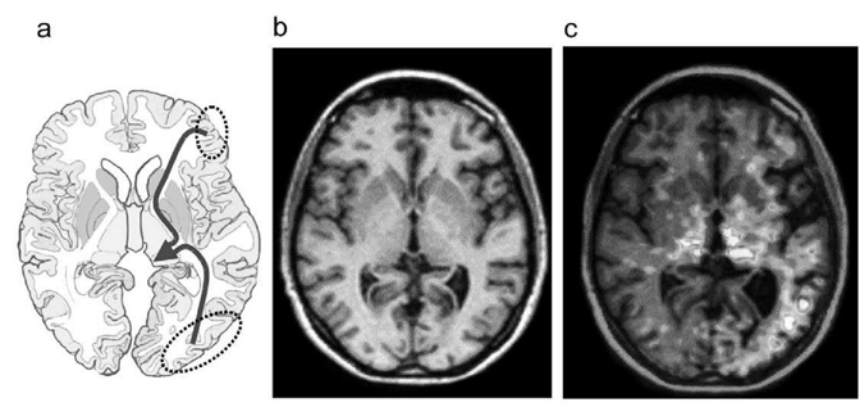
2015

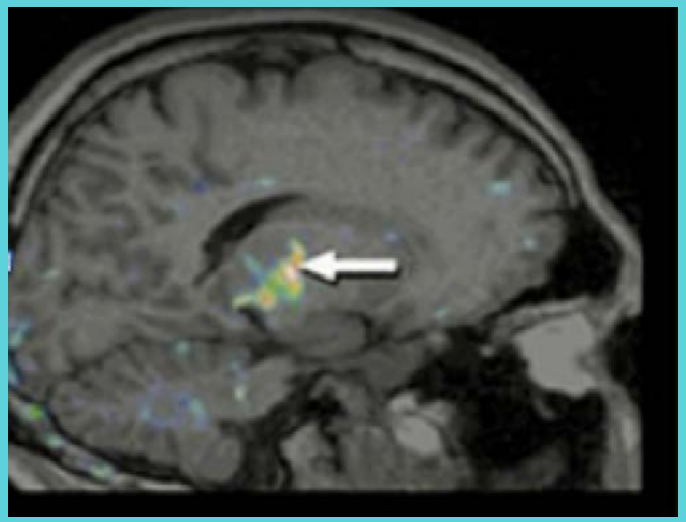
Glia and Neuroinflammation

Brain plasticity and microglia: is transsynaptic glial activation in the thalamus after limb denervation linked to cortical plasticity and central sensitisation?

Banati RB.

J Physiol Paris. 2002 Apr-Jun;96(3-4):289-99.



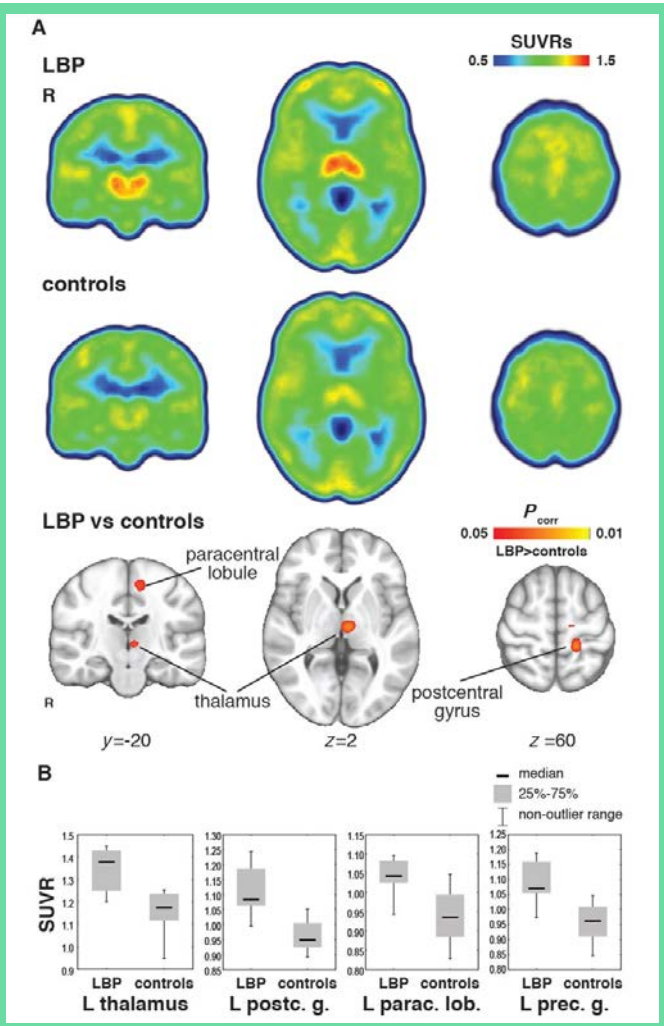


2002

Evidence for brain glial activation in chronic pain patients.

Loggia ML, Chonde DB, Akeju O, Arabasz G, Catana C, Edwards RR, Hill E, Hsu S, Izquierdo-Garcia D, Ji RR, Riley M, Wasan AD, Zürcher NR, Albrecht DS, Vangel MG, Rosen BR, Napadow V, Hooker JM.

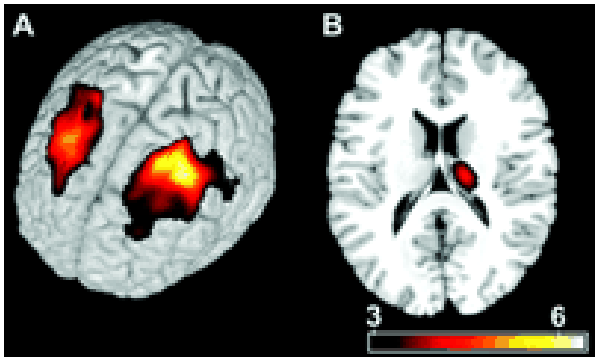
Brain. 2015 Mar;138(Pt 3):604-15.



2015

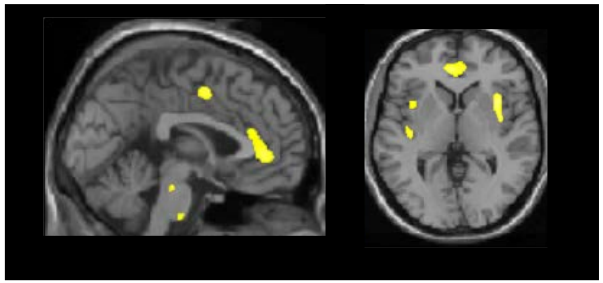
Gray Matter Changes

Chronic back pain is associated with decreased prefrontal and thalamic gray matter density.
Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR.
J Neurosci. 2004 Nov 17;24(46):10410-5.

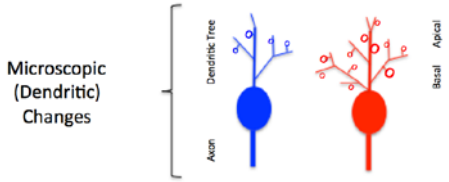


2004

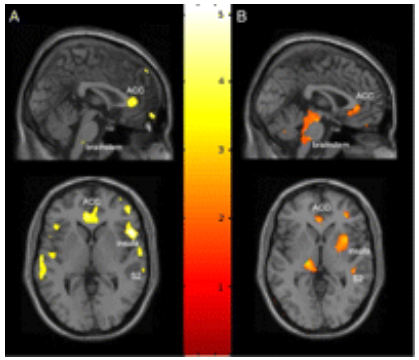
Gray matter decrease in patients with chronic tension type headache.
Schmidt-Wilcke T, Leinisch E, Straube A, Kämpfe N, Draganski B, Diener HC, Bogdahn U, May A.
Neurology. 2005 Nov 8;65(9):1483-6.



2005

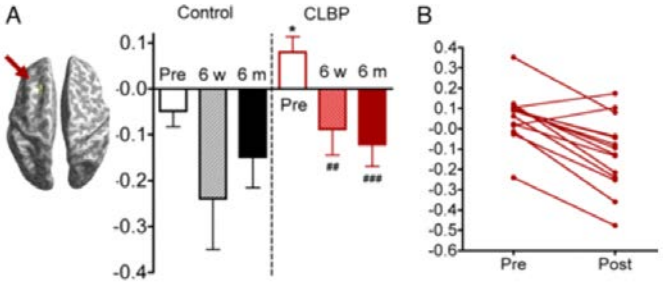


Brain gray matter decrease in chronic pain is the consequence and not the cause of pain.
Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A.
J Neurosci. 2009 Nov 4;29(44):13746-50.



2009

Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function.
Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, Jarzem P, Bushnell MC, Shir Y, Ouellet JA, Stone LS.
J Neurosci. 2011 May 18;31(20):7540-50.



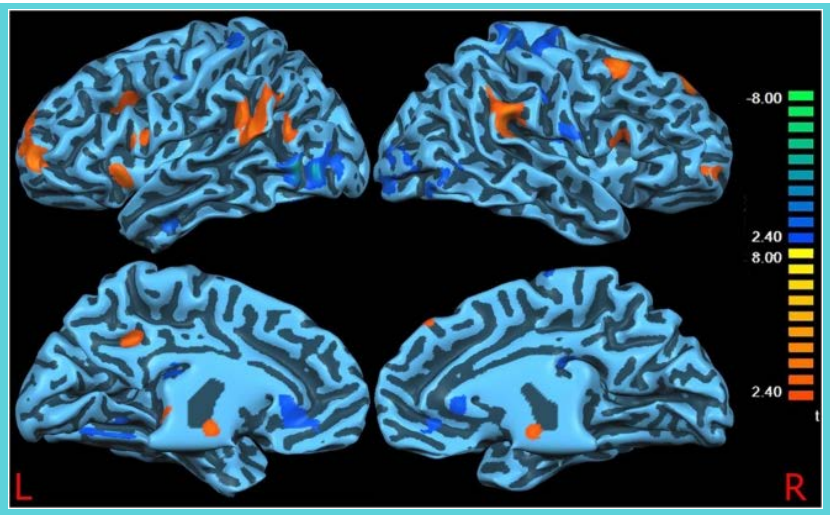
2011

Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain.
Seminowicz DA, Shpaner M, Keaser ML, Krauthamer GM, Mantegna J, Dumas JA, Newhouse PA, Filippi CG, Keefe FJ, Naylor MR.
J Pain. 2013 Dec;14(12):1573-84.

2013

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.
PLoS One. 2009;



2009

Orofacial Neuropathic pain

Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes.
Gustin SM, Peck CC, Wilcox SL, Nash PG, Murray GM, Henderson LA.
J Neurosci. 2011 Apr 20;31(16):5956-64.

2011

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.
Hum Brain Mapp. 2013 Oct;34(10):2733-46.

2013

Post-herpetic Neuralgia

Self-regulation of brain activity in patients with postherpetic neuralgia: a double-blind randomized study using real-time FMRI neurofeedback.
Guan M, Ma L, Li L, Yan B, Zhao L, Tong L, Dou S, Xia L, Wang M, Shi D.
PLoS One. 2015 Apr 7;10(4):e0123675.

2015

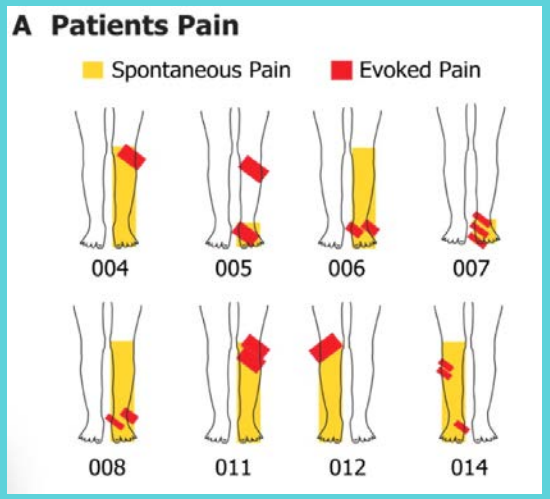
Small Fiber Neuropathy

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**

2015

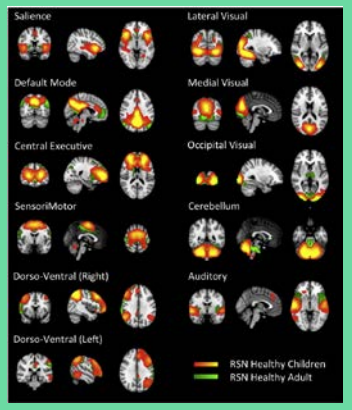
Pain In Children

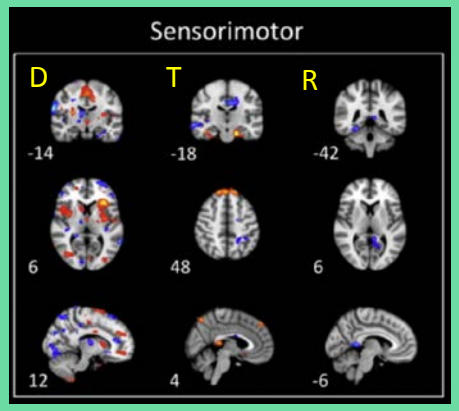
fMRI reveals distinct CNS processing during symptomatic and recovered complex regional pain syndrome in children.
Lebel A, Becerra L, Wallin D, Moulton EA, Morris S, Pendse G, Jasciewicz J, Stein M, Aiello-Lammens M, Grant E, Berde C, Borsook D.
Brain. 2008 Jul;131(Pt 7):1854-79.



2010

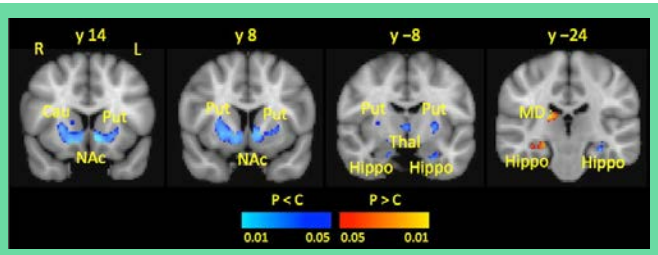
Intrinsic brain networks normalize with treatment in pediatric complex regional pain syndrome.
Becerra L, Sava S, Simons LE, Drosos AM, Sethna N, Berde C, Lebel AA, Borsook D.
Neuroimage Clin. 2014 Aug 10;6:347-69.

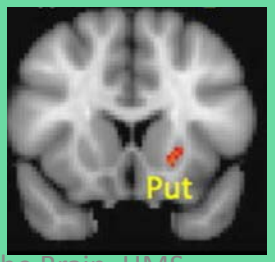


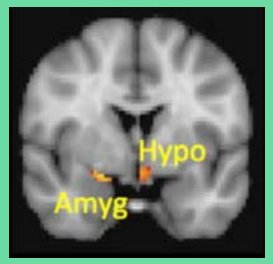


2014

Rapid treatment-induced brain changes in pediatric CRPS.
Erpelding N, Simons L, Lebel A, Serrano P, Pielech M, Prabhu S, Becerra L, Borsook D.
Brain Struct Funct. 2014 Dec 17.



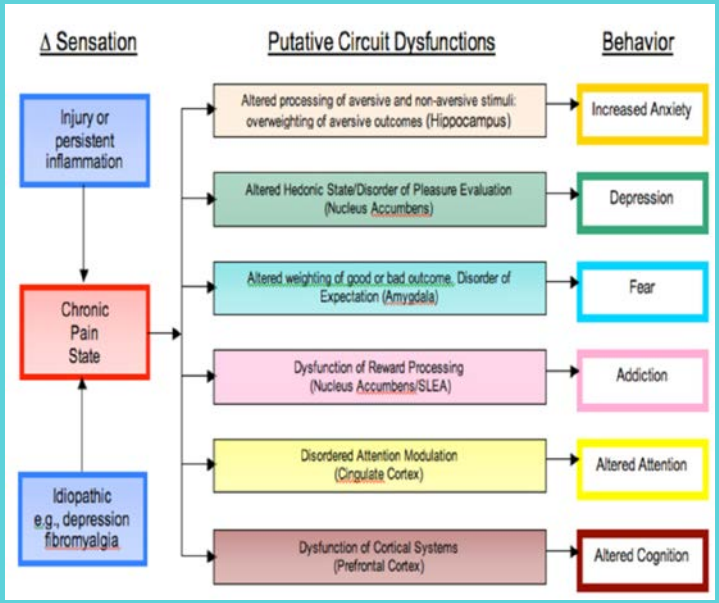




2014

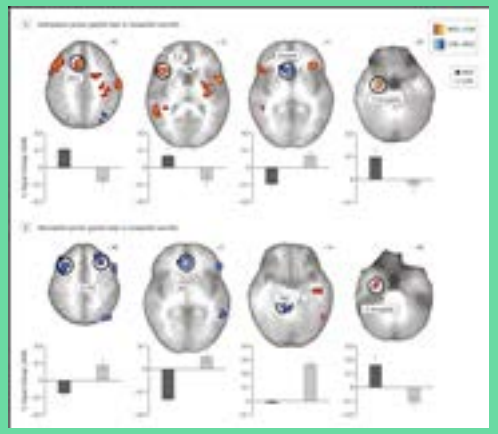
Psychiatric Disease and Pain

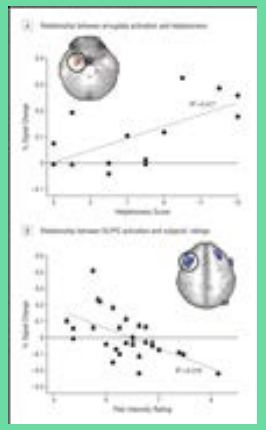
Reward-aversion circuitry in analgesia and pain: implications for psychiatric disorders.
Borsook D, Becerra L, Carlezon WA Jr, Shaw M, Renshaw P, Elman I, Levine J.
Eur J Pain. 2007 Jan;11(1):7-20.



2007

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.





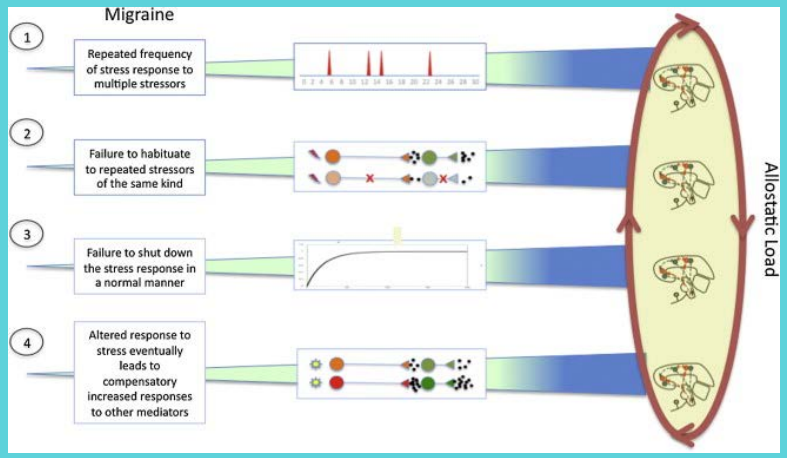
2008

Pain and suicidality: insights from reward and addiction neuroscience.
Elman I, Borsook D, Volkow ND.
Prog Neurobiol. 2013 Oct;109:1-27

2013

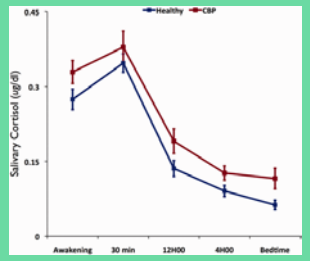
Stress and Pain

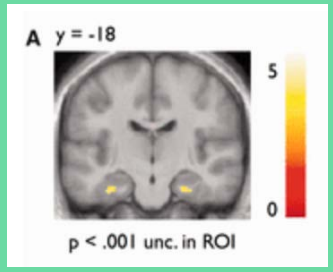
Understanding migraine through the lens of maladaptive stress responses: a model disease of allostatic load.
Borsook D, Maleki N, Becerra L, McEwen B.
Neuron. 2012 Jan 26;73(2):219-34.



2012

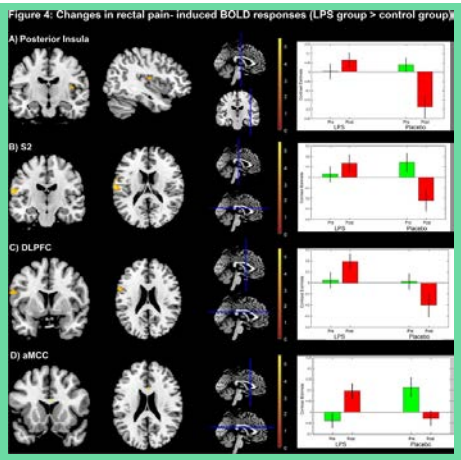
The stress model of chronic pain: evidence from basal cortisol and hippocampal structure and function in humans.
Vachon-Presseau E, Roy M, Martel MO, Caron E, Marin MF, Chen J, Albouy G, Plante I, Sullivan MJ, Lupien SJ, Rainville P.
Brain. 2013 Mar;136(Pt 3):815-27





2013

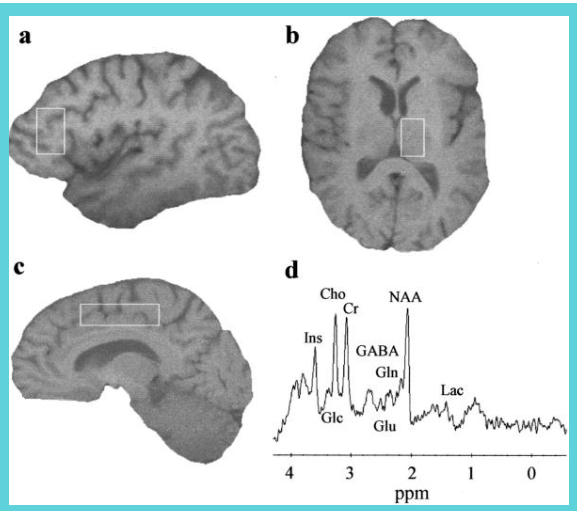
Neural circuitry mediating inflammation-induced central pain amplification in human experimental endotoxemia.
Benson S, Rebernik L, Wegner A, Kleine-Borgmann J, Engler H, Schlamann M, Forsting M, Schedlowski M, Elsenbruch S.
Brain Behav Immun. 2015 Apr 14. pii: S0889-1591(15)00111-7

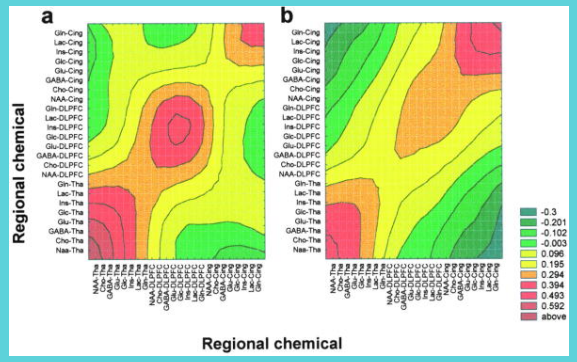


2015

Chemical Markers (MRS)

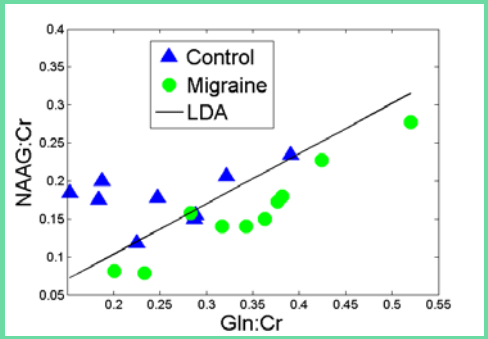
Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study.
Grachev ID, Fredrickson BE, Apkarian AV.
Pain. 2000 Dec 15;89(1):7-18.





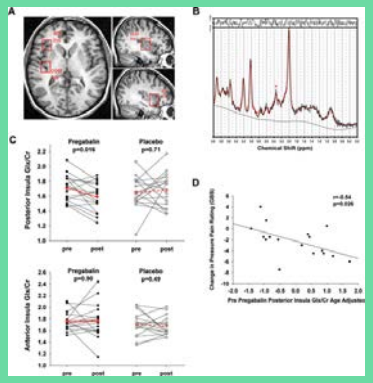
2000

Excitatory neurotransmitters in brain regions in interictal migraine patients.
Prescot A, Becerra L, Pendse G, Tully S, Jensen E, Hargreaves R, Renshaw P, Burstein R, Borsook D.
Mol Pain. 2009 Jun 30;5:34.



2009

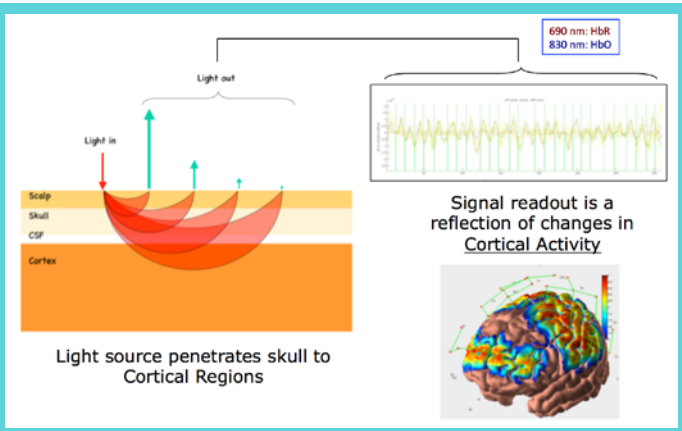
Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients.
Harris RE, Napadow V, Huggins JP, Pauer L, Kim J, Hampson J, Sundgren PC, Foerster B, Petrou M, Schmidt-Wilcke T, Clauw DJ.
Anesthesiology. 2013 Dec;119(6):1453-64.

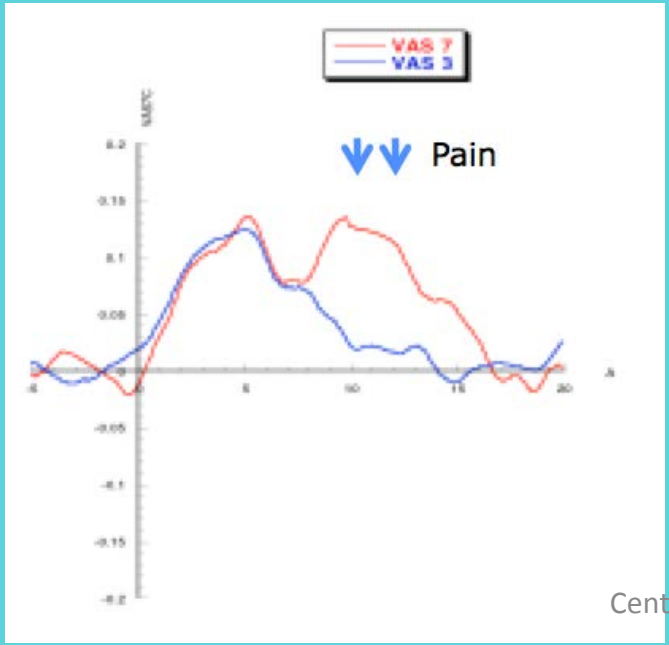


2013

Pain Measures in the Operating Room

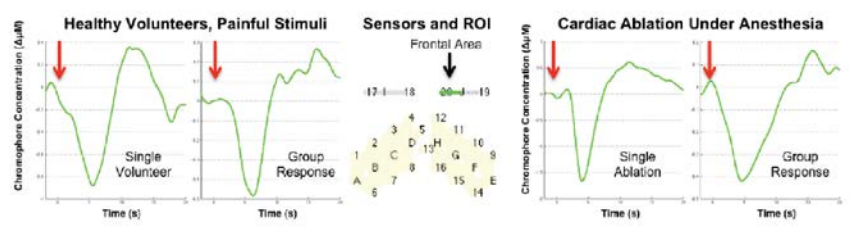
Diffuse optical tomography of pain and tactile stimulation: activation in cortical sensory and emotional systems.
Becerra L, Harris W, Joseph D, Huppert T, Boas DA, Borsook D.
Neuroimage. 2008 Jun;41(2):252-9.

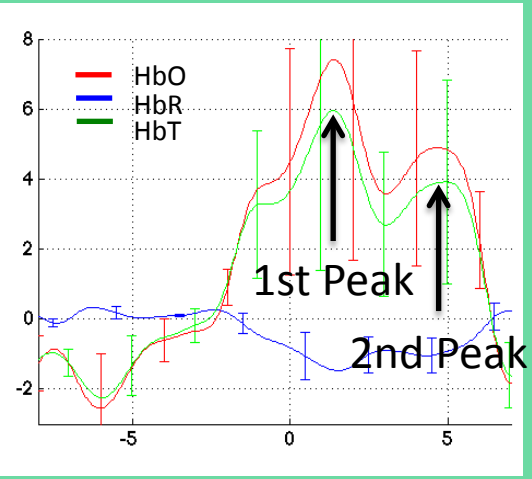




2008

TBD



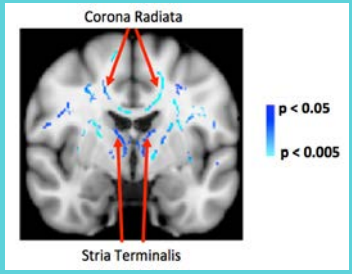


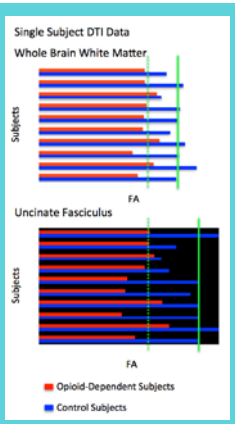
2015

Opioids Change the Brain

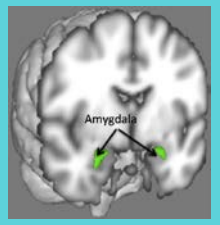
Alterations in brain structure and functional connectivity in prescription opioid-dependent patients.
Upadhyay J, Maleki N, Potter J, Elman I, Rudrauf D, Knudsen J, Wallin D, Pendse G, McDonald L, Griffin M, Anderson J, Nutile L, Renshaw P, Weiss R, Becerra L, Borsook D.
Brain. 2010 Jul;133(Pt 7):2098-114.

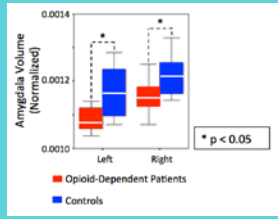
DTI



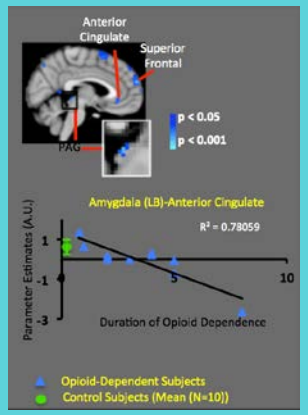


Gray Matter





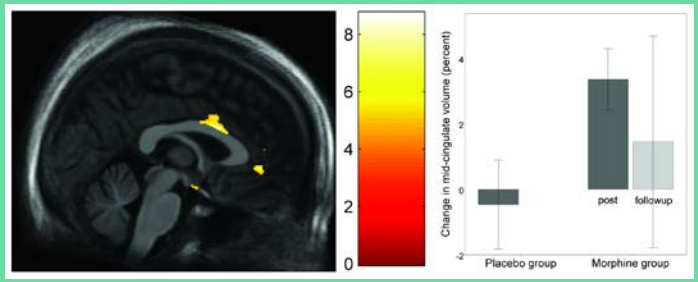
Functional Conn.



2010

2010

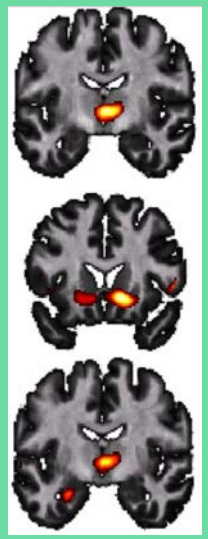
Prescription opioid analgesics rapidly change the human brain.
Younger JW, Chu LF, D'Arcy NT, Trott KE, Jastrzab LE, Mackey SC.
Pain. **2011** Aug;152(8):1803-10.2010



2011

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

Increased



Decreased

2013

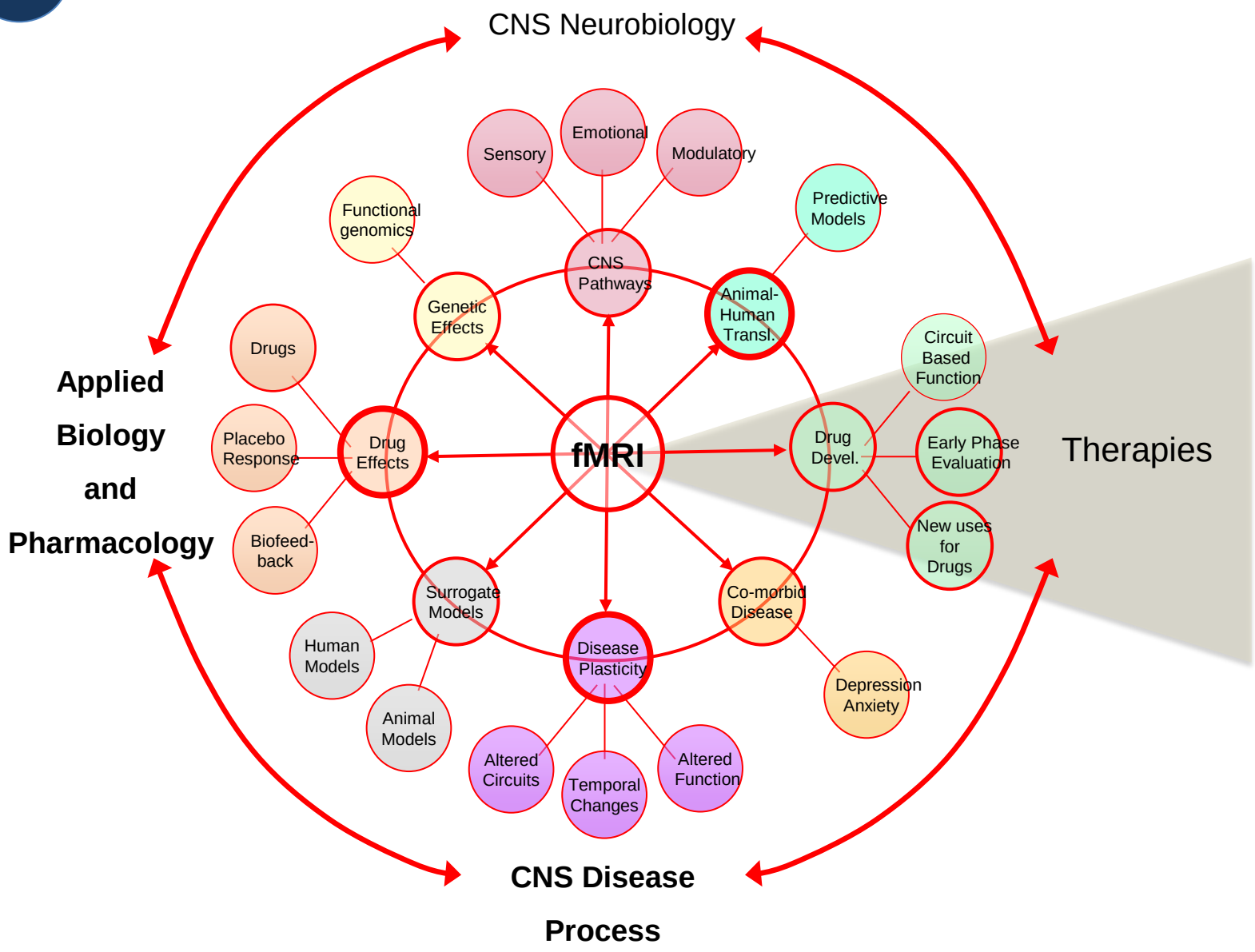
Main Pointers: Chronic Pain

- 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

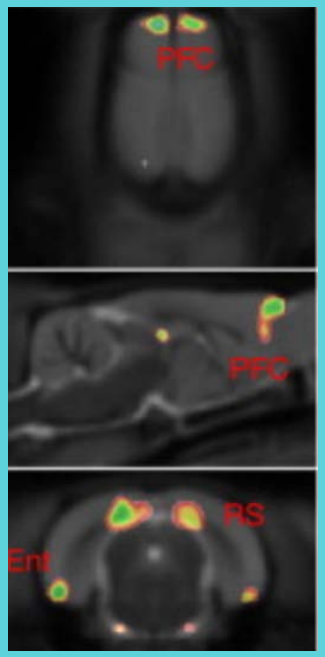
- Imaging Transforms the treatment of our patients
  - Predicting Pain and Treatment
  - Measure pain in the OR
  - Evaluate the long term effects of drugs

4


CNS Neurobiology
Sensory
Emotional
Modulatory
Functional genomics
Predictive Models
CNS Pathways
Genetic Effects
Animal-Human Transl.
Drugs
Circuit Based Function
Applied Biology and Pharmacology
Placebo Response
Drug Effects
fMRI
Drug Devel.
Early Phase Evaluation
Therapies
Biofeed-back
New uses for Drugs
Surrogate Models
Co-morbid Disease
Human Models
Disease Plasticity
Depression Anxiety
Animal Models
Altered Circuits
Temporal Changes
Altered Function
CNS Disease Process

Translational Imaging I: Structure and Function

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.
Neuroimage. 2009 Sep;47(3):1007-14.



2009

CNS activation maps in awake rats exposed to thermal stimuli to the dorsum of the hindpaw.
Becerra L, Chang PC, Bishop J, Borsook D.
Neuroimage. 2011 Jan 15;54(2):1355-66.

2011

Robust reproducible resting state networks in the awake rodent brain.
Becerra L, Pendse G, Chang PC, Bishop J, Borsook D.
PLoS One. 2011;6(10):e25701.

2011

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.
Pain. 2014 Jun;155(6):1128-39.

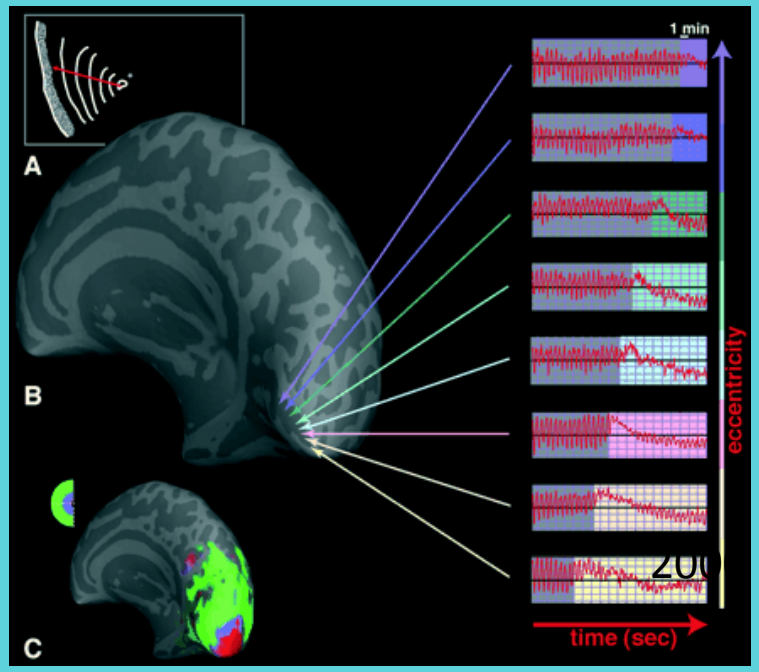
2014

Metabolic brain activity suggestive of persistent pain in a rat model of neuropathic pain.
Thompson SJ, Millecamps M, Aliaga A, Seminowicz DA, Low LA, Bedell BJ, Stone LS, Schweinhardt P, Bushnell MC.
Neuroimage. 2014 May 1;91:344-52.

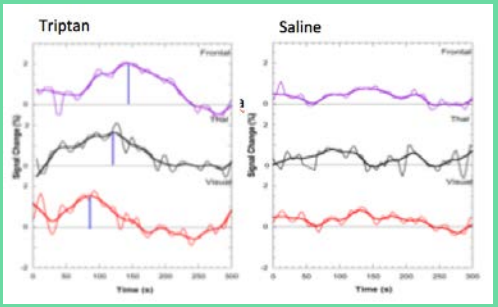
2014

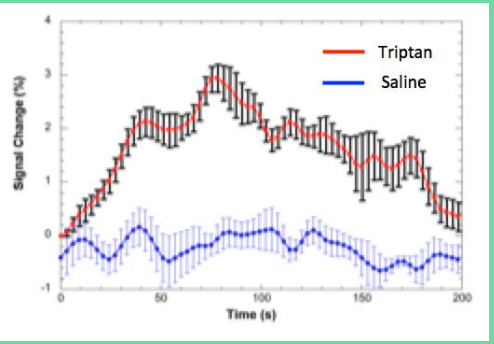
Translational Imaging II: An Example - Capturing Cortical Spreading Depression

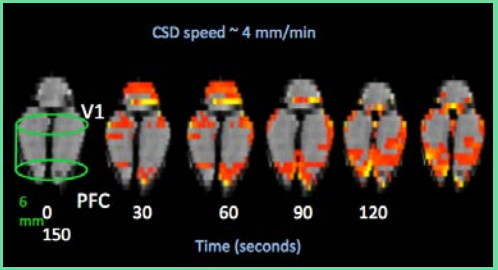
Mechanisms of **migraine aura** revealed by functional MRI in human visual cortex.
Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, Kwong KK, Cutrer FM, Rosen BR, Tootell RB, Sorensen AG, Moskowitz MA.
Proc Natl Acad Sci U S A. 2001 Apr 10;98(8):4687-92.



2001







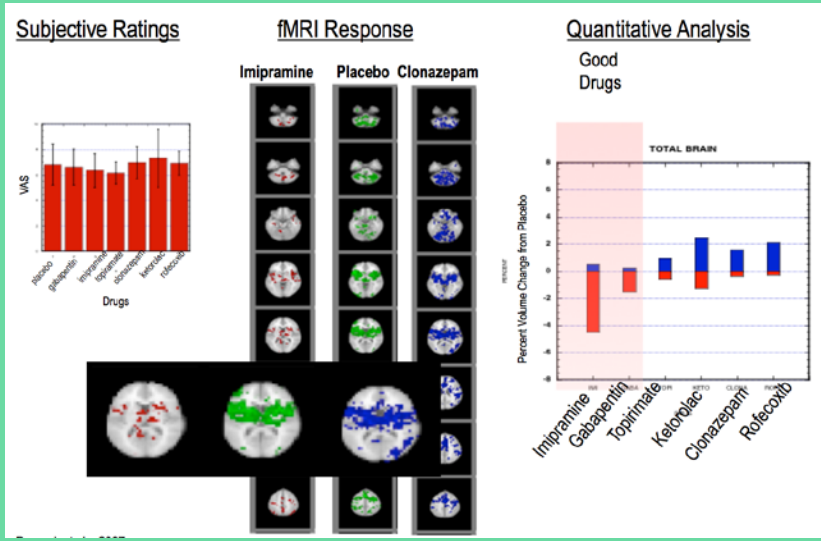
Becerra et al., In Submission

Translational Models III: Drugs and Circuits

CNS response to a thermal stressor in human volunteers and rats may predict the clinical utility of analgesics

David Borsook[1,2,*], Gautam Pendse[1], Mathew Aiello-Lammens[1], Marcie Glicksman[3], Julie Gostic[1], Seth Sherman[1], Joshua Korn[1], Marnie Shaw[1], Ken Stewart[1], Richard Gostic[1], Shelly Bazes[1], Richard Hargreaves[4] and Lino Becerra[1]

Drug Development Research, Feb 2007 23–41,

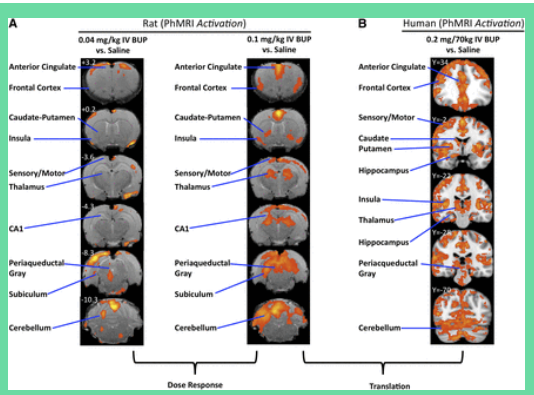


2007

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

Becerra L, Upadhyay J, Chang PC, Bishop J, Anderson J, Baumgartner R, Schwarz AJ, Coimbra A, Wallin D, Nutile L, George E, Maier G, Sunkaraneni S, Iyengar S, Evelhoch JL, Bleakman D, Hargreaves R, **Borsook** D.

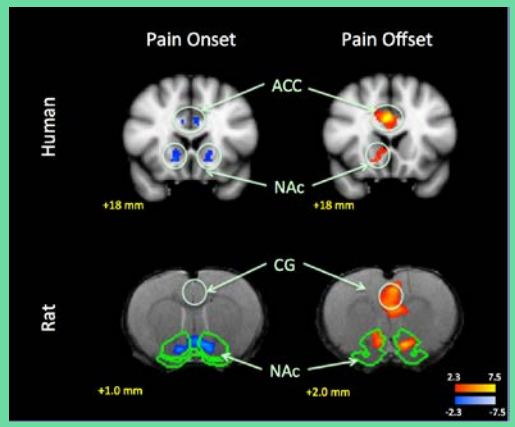
J Pharmacol Exp Ther. 2013 Apr;345(1):41-51.



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.

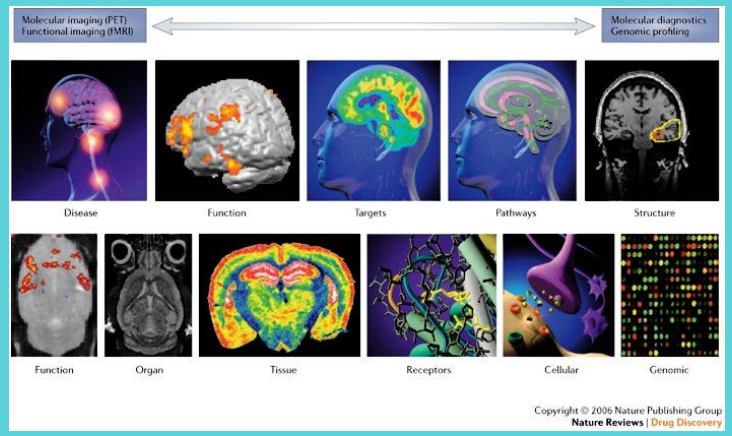
J Neurophysiol. 2013 Sep;110(5):1221-6.



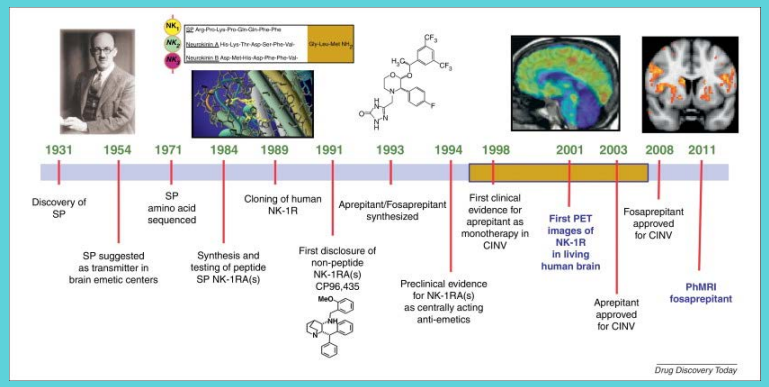
2013

Drug Development I

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

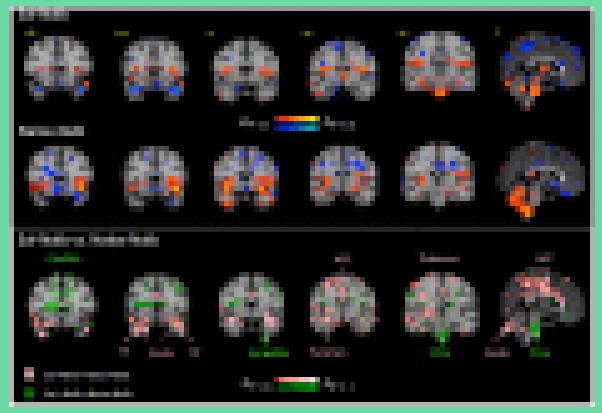


Decision-making using fMRI in clinical drug development: revisiting NK-1 receptor antagonists for pain.
Borsook D, Upadhyay J, Klimas M, Schwarz AJ, Coimbra A, Baumgartner R, George E, Potter WZ, Large T, Bleakman D, Evelhoch J, Iyengar S, Becerra L, Hargreaves RJ.
Drug Discov Today. 2012 Sep;17(17-18):964-73.



Pain facilitation brain regions activated by nalbuphine are revealed by pharmacological fMRI.
Gear R, Becerra L, Upadhyay J, Bishop J, Wallin D, Pendse G, **Levine J**, Borsook D.
PLoS One. 2013;8(1):e50169.

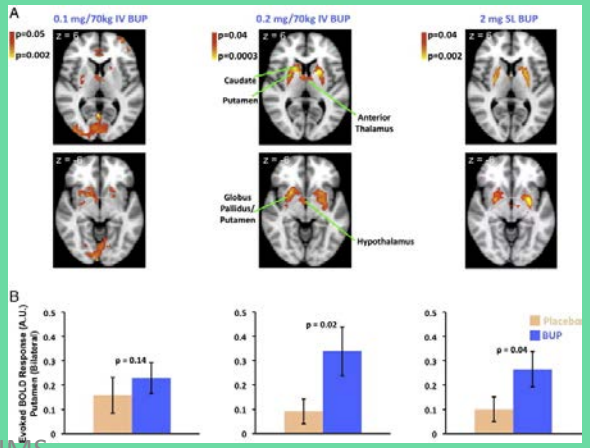
Dissecting Drugs



2013

Modulation of CNS pain circuitry by intravenous and sublingual doses of buprenorphine.
Upadhyay J, Anderson J, Baumgartner R, Coimbra A, Schwarz AJ, Pendse G, Wallin D, Nutile L, Bishop J, George E, Elman I, Sunkaraneni S, Maier G, Iyengar S, Evelhoch JL, Bleakman D, Hargreaves R, Becerra L, Borsook D.
Neuroimage. 2012 Feb 15;59(4):3762-73.

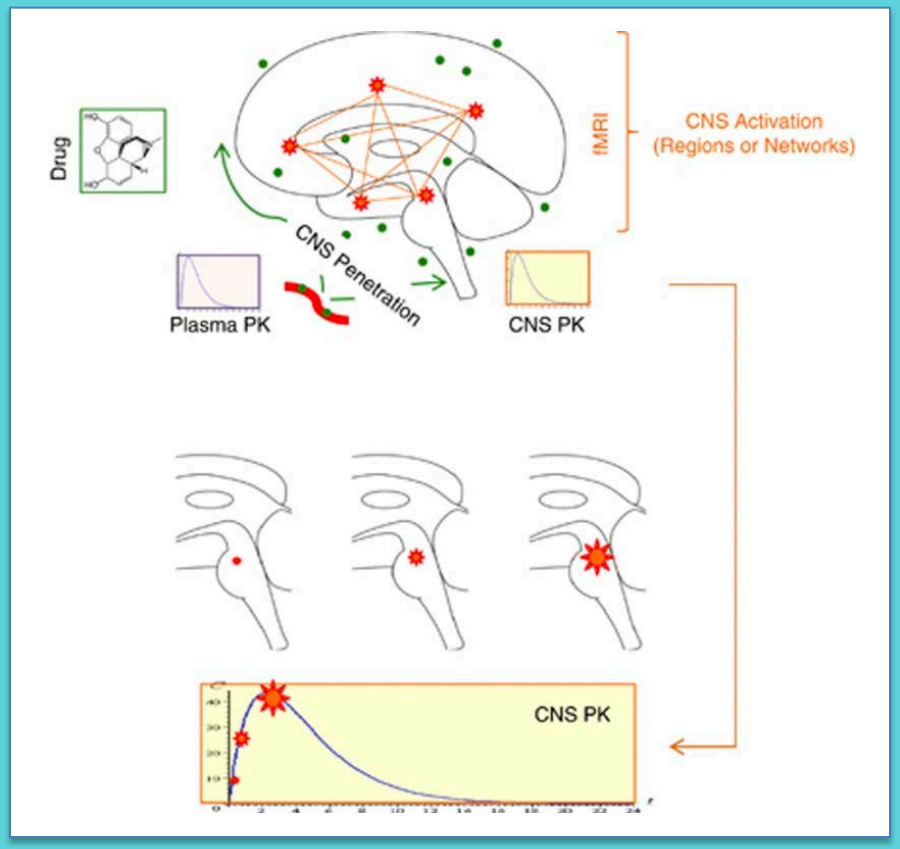
CNS Dosing



2012

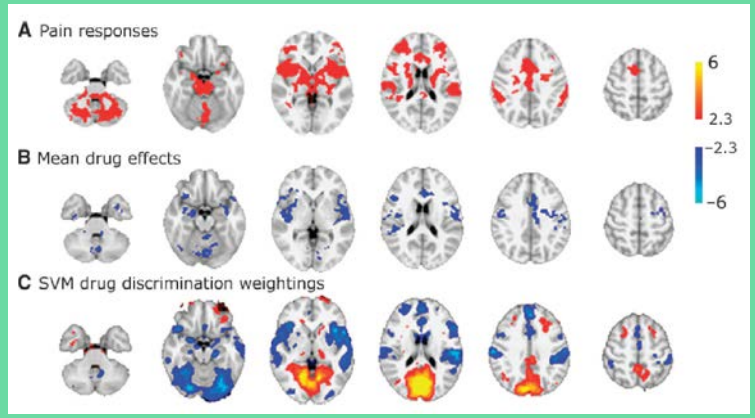
Drug Development

Use of functional imaging across clinical phases in CNS drug development.
Borsook D, Becerra L, Fava M.
Transl Psychiatry. 2013 Jul 16;3:e282.



2013

Learning to identify CNS drug action and efficacy using multistudy fMRI data.
Duff EP, Vennart W, Wise RG, Howard MA, Harris RE, Lee M, Wartolowska K, Wanigasekera V, Wilson FJ, Whitlock M, Tracey I, Woolrich MW, Smith SM.
Sci Transl Med. 2015 Feb 11;7(274):274ra16



machine learning methods and data from multiple published studies to assess new data

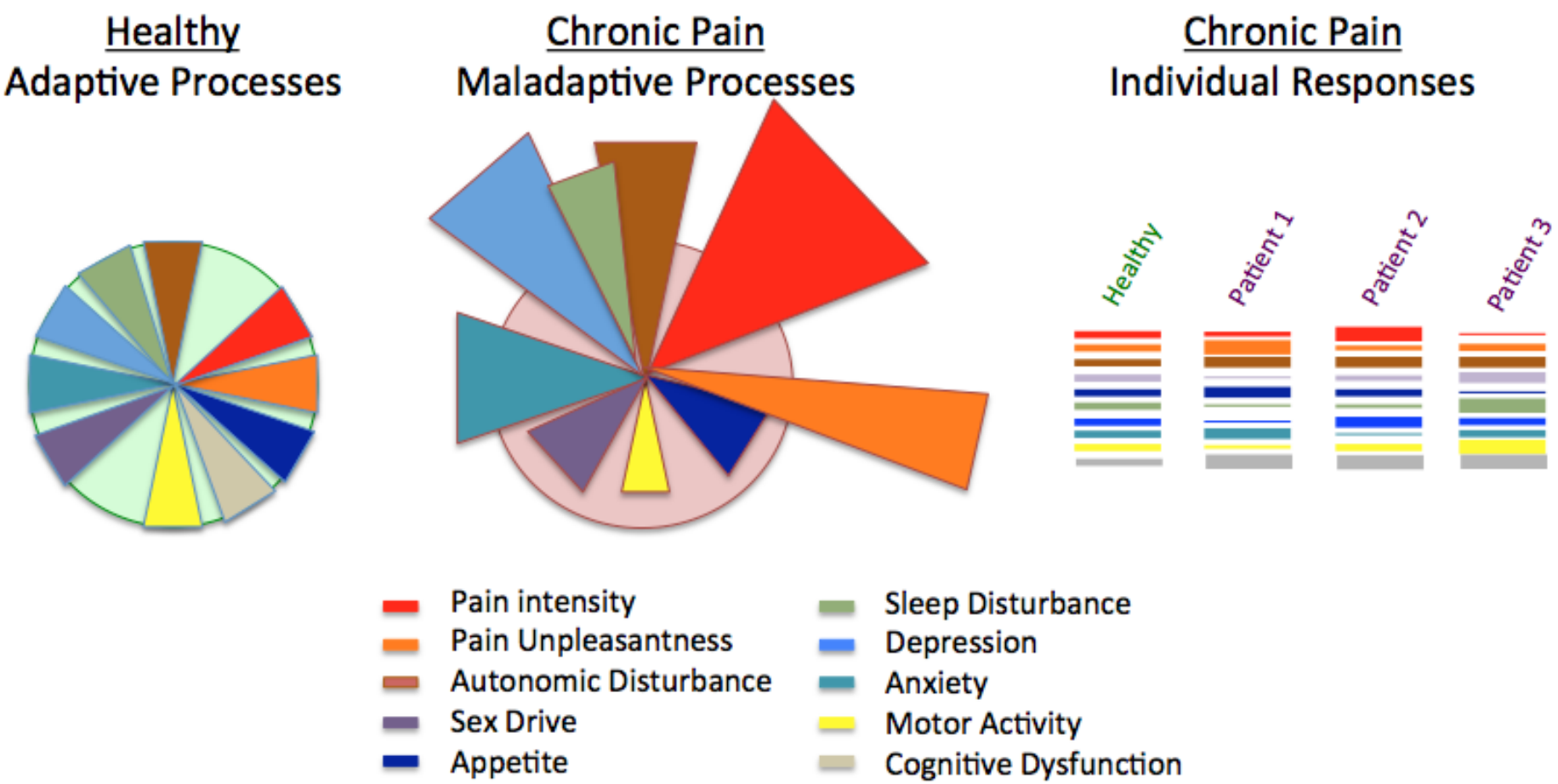
2013

Pharmacologic modulation of hand pain in osteoarthritis: a double-blind placebo-controlled functional magnetic resonance imaging study using naproxen.
Sanders D, Krause K, O'Muircheartaigh J, Thacker MA, Huggins JP, Vennart W, Massat NJ, Choy E, Williams SC, Howard MA.
Arthritis Rheumatol. 2015 Mar;67(3):741-51

2015

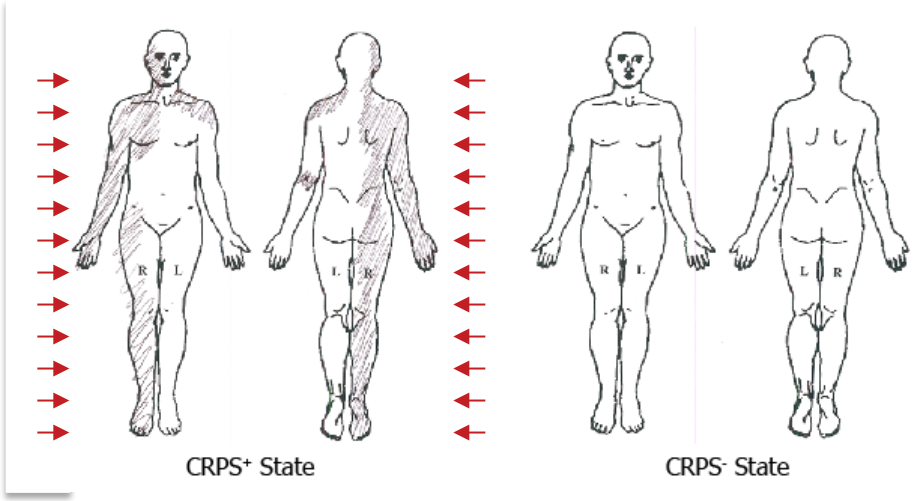
Main Pointers: Translational Aspects

- 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)

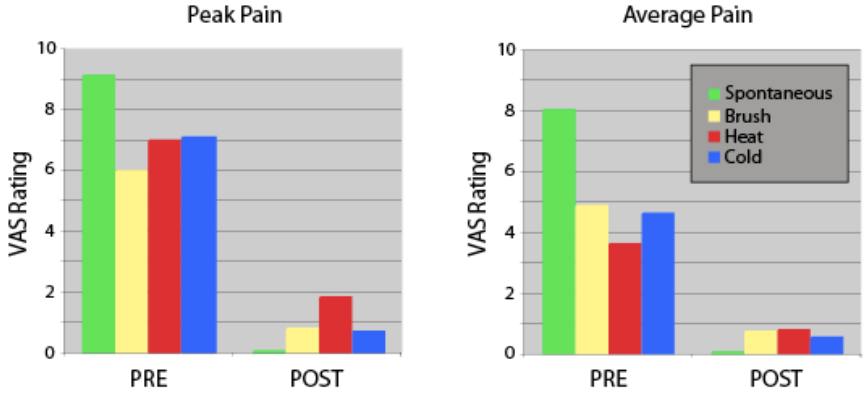


Borsook and Kalso, 2013

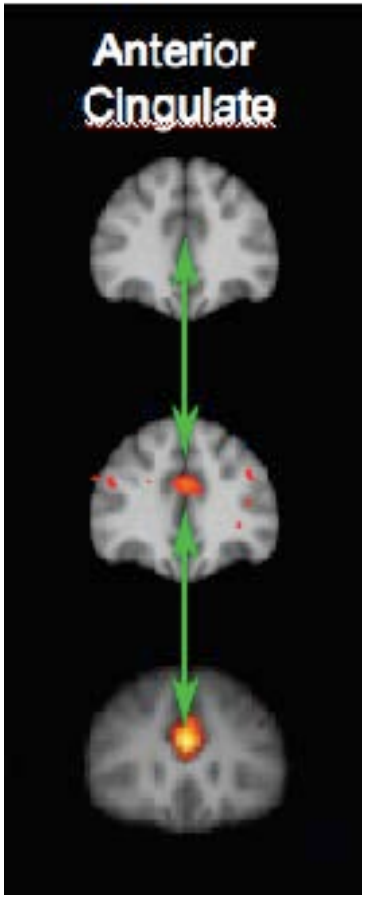
Clinical Presentation

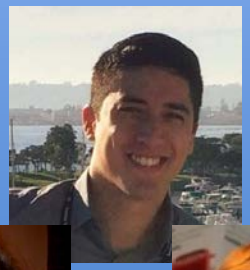
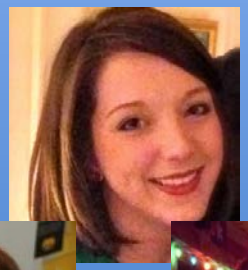


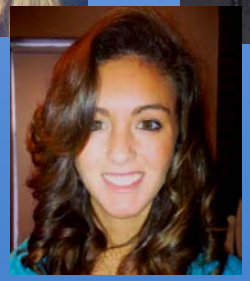
Psychophysics



Resting State Networks





Current and Recent Support by:

NIH (NINDS, NCCIH, NIGMS, NIDA, NICHD)

R01 NS073997 (DB)
R01 NS075018 (DB)
R21AT007530 (DB)
K24 NS064050 (DB)
R01 GM104986 (DBo/DB)
DOD (DB)

Foundations

Mayday Fund
Migraine Research Foundation
National Headache Foundation

Philanthropy

Mayday Louis Herlands Research Chair
Private Donors

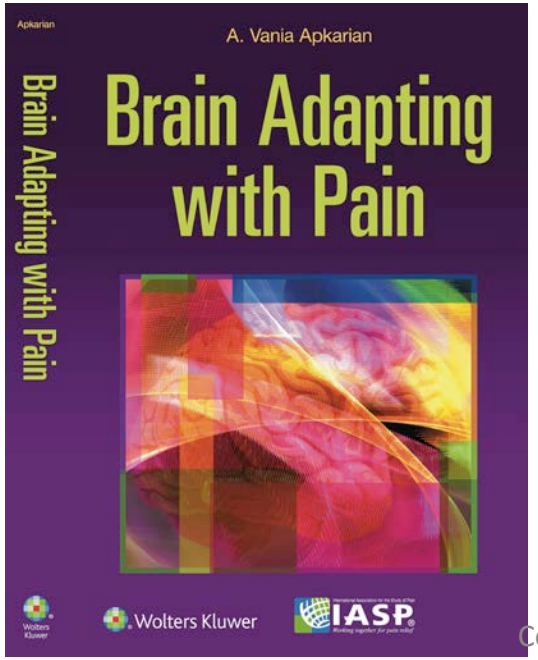
Current Contributors:

Lino Becerra
Rami Burstein
Clas Linnman
Laura Simons
Nadia Barakat
Dusica Bajic
Eric Moulton
Sophie Wilcox
Duncan Hodkinson
Nathalie Erpelding
Vanda Faria
Ellen Grant
Alyssa LeBel
Robert Wolff
Steven Scrivani
Damian Fair
Edita Navaratilova
Jennifer Xie
Rosanna Veggeberg
Paul Serano
Allison Ludwick

Northwestern University Medical School
Chicago, Illinois

Professor of Physiology, Surgery, Anesthesia, Cognitive Brain Mapping Group, & Neuroscience Institute

>144 Peer Reviewed Papers



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.