Neuroimaging Biomarkers for Pain

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Disclosures – Funding Sources

- National Center of Complementary and Alternative Medicine
  - P01 AT006651-01
- National Institutes of Drug Abuse (NIDA)
  - K24 DA029262, R21 DA026092
- National Institutes of Neurological Diseases and Syndromes
  - R01 NS053961
- National Institutes of Diabetes and Digestive and Kidney Diseases
  - U01 DK082316
- Dodie and John Rosekrans Pain Research Endowment
- Redlich Pain Research Endowment
- Stanford NeuroVentures - BioX
- No industry conflicts

Experiences With Pain – Institute of Medicine Report

- Affects 100 Million Americans
  - More than heart disease, diabetes and cancer combined
- Indirect/direct medical expenses
  - US $560-$630 Billion/year
  - $100 billion/year in Medicare funding alone
- Pain can become a disease in its own right through changes in the CNS
Descartes’ View of Pain (1664)

- Dualism
- Descartes viewed the world as mechanistic and viewed human behavior in terms of reflexive mechanisms elicited by stimuli in the environment
- Fire pulled on “delicate threads” that opened pores in the commonsense center

Pain is Not Equal to Nociception

Pain is a Product of the Prain

- Cognition: attention, distraction, hypervigilance, catastrophizing, re-appraisal, hypnotic suggestion
- Mood: depression, anxiety, catastrophizing, emotional context
- Context: beliefs, expectations, placebo, motivation
- Individual differences: genetics, gender, history of injury, atrophy
Individual Differences in Pain Sensitivity

- 500 healthy volunteers
- 49°C stimulus
- Over 300 mouse genes found to modulate pain sensitivity and analgesia. Over 20 human SNPs
  - Genes thought to account for 20%-50% of variability of pain
  - Women slightly (8%) more sensitive to heat pain.
- Ethnicity
- Anxiety, catastrophizing, somatization
- What about the role of the brain?

Kim H, et al, Pain 2004
Seminowicz DA, et al, Pain 2006
Pain Genesdb http://www.jbldesign.com/jmogil/enter.html

Individual Differences in the Experience of Pain

- 49°C stimuli
- High vs low sensitivity subjects
- High sensitivity → more activation
  - Caudal and perigenual ACC
  - Primary somatosensory cortex
  - Prefrontal cortex
Pain - Fear and Anxiety

- Individual’s anxiety about, and fear of, painful sensations predicts physical complaints and treatment outcomes in patients with chronic pain (McCraeke, 1998, 1999).
- Patients high in anxiety more likely to develop post-herpetic neuralgia (Dworkin, 1992).
- Patients higher in fear and anxiety more likely to develop increased pain after surgery or injury (Granot, 2005).
- Psychological construct? But why? What are the neurophysiological underpinnings?

Individual difference in pain – Effects of fear of pain

- Right Lateral Orbital frontal activation may reflect attempts by fearful individuals to evaluate and/or regulate possible responses to painful stimuli.

Neuroimaging of Clinical Pain Conditions

The Role of Brain Plasticity
Chronic low back pain causes premature brain gray matter atrophy

- Age related losses in gray matter = 0.5%/year
- Chronic low back pain patients = 5.4% decrease
- Reduced in bilateral prefrontal cortex and right thalamus
- Impact of chronic low back pain is an additional 10 years of brain atrophy
- Duration of chronic low back pain is a strong predictor of gray matter changes


Resting-State Functional Connectivity

- Brain activity continues in the absence of an externally-cued task
- Any brain region will therefore have spontaneous fluctuations in BOLD signal
- A brain region’s “resting” BOLD signal timecourse can be used as the regressor
- Many resting state networks identified with different proposed functions.

Differences in Default Mode Network between Patients and Controls

- 8 diabetic neuropathic pain patients and 8 healthy controls
- Regions with reduced connectivity in patients:
  - Left fusiform gyrus, left lingual gyrus, left inferior temporal gyrus, right inferior occipital, DACC, bilateral pre and post central gyri
- Regions with greater connectivity in patients:
  - Left precuneus, DLPFC, Thalami, Insulae, right mammillary body

Functional Connectivity of Default Mode Network
Increased in Patients with Fibromyalgia

- Increased Connectivity in DMN in Fibromyalgia in sensory/pain related areas

Are These Brain Changes Reversible and What are the Effects of Treatment?

- Chronic Low Back Pain Related Brain Changes Reverse After Treatment
  - 18 patients with chronic low back pain
  - Structural scans and Cognitive tasks at baseline and 6mths after treatment (spine surgery or facet joint injections)
  - After treatment increased cortical thickness in the left dIPFC
  - Increased dIPFC correlated with pain reduction and disability
  - Left dIPFC activity during attention task was abnormal before TX, but normalized after TX

Prescription Opioids Rapidly Change the Human Brain

- 10 patients with low back pain on long acting opioids
- Decreased gray matter in right amygdala
- Increased gray matter in dorsal posterior cingulate, left inferior frontal gyrus, hypothalamus, and pons
- Gray matter atrophy and hypertrophy significantly correlated with morphine dosage

Younger, Chu, D’Arcy, Trott and Mackey (Pain, 2011)

Future Directions: Pain Detection and Pain Biomarkers

Need for Objective Biomarkers of Pain

- Currently rely on self-report of pain and remains the gold standard
- Vulnerable populations
  - Very young
  - Older patients with dementia
  - ICU patients
- Legal system - Thousands of cases each year based on pain and suffering (personal injury, workers comp, med-mal)
- Objective biomarkers
  - Treatment targets
  - Treatment response
- Efforts: HR, Skin Conductance, EEG
- Can we use brain imaging to elucidate the “truth”?

- Training (8 subjects)
  - Painful
  - Non-Painful

- Testing (16 novel subjects)
  - Painful
  - Non-Painful

<< Each map of BOLD signal is plotted in feature space. 
<< A boundary line is defined, separating maps associated with painful and non-painful stimulation. 
<< Novel maps are plotted into the feature space. 
<< Stimuli are classified as painful or non-painful by comparing maps of BOLD signal to the boundary line. 

Mackey In Review
Presented at IASP

Detecting Pain from Brain Activity

- 24 healthy subjects
- Trained on 8 subjects, tested on 2 independent groups of 16 subjects (8 each group).
- 14 painful thermal stimuli and 14 non-painful thermal stimuli applied to the left forearm
- S2 had highest discriminant value
- 87% overall accuracy

Chatterjee N, Brown J, Younger J, and Mackey S, PLOS One (2011)
Future Directions

- Neuroimaging of the CNS is advancing our understanding of these mechanisms and pointing the way to future therapeutic targets (e.g., pharmacologic, stimulation, mind-body).
- Personalized pain medicine
- Pain Detection:
  - Identify differences between pain and related conditions such as affective disorders.
  - Investigate different pain conditions to determine commonality.
  - Characterize ability to distinguish physical pain from imagined pain, pain deception, empathy of pain, remembered pain, etc.
  - Incorporate multimodal imaging techniques to improve classification. Also combine with genomics and other biomarkers.
- Keep this technology from being abused.

Stanford Systems Neuroscience and Pain Lab (SNAPL)

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"We study the best things on Earth that hurt"

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