Brain Imaging and Neuroplasticity in “Strange” Pain Disorders: Phantom Limb Pain Complex Regional Pain Syndromes (CRPS) Fibromyalgia

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Disclosure

• Children’s Hospital Boston, Dr. Berde, and colleagues have patents, ongoing technology transfer, research support and potential future royalties with two companies, WEX and Proteus, related to prolonged duration local anesthetics.

• Nothing in this lecture will have any overlap with prolonged local anesthesia or any other potential conflicts of interest.
“Strange” Pain Disorders:

Phantom Limb Pain
CRPS/RSD
Fibromyalgia
Painful Focal Dystonias
Pain as a “habit” or “memory trace”
Conversion or somatoform disorders
Acknowledgments

- A number of fMRI slides are copied from the Oxford fMRI physics website and from papers by Vania Apkarian and colleagues, summarized in the journal Pain, March 2011 issue.

- Don’t worry, some of these slides are for reference purposes; we won’t show all of them in the lecture.
Acknowledgments

• One of us (Dr. Berde) is not an expert in brain imaging, so Dr. Berde’s portions of the lecture are from the viewpoint of a collaborator who works with imaging experts, not an expert.

• Both of us have learned from our collaborators: David Borsook, Lino Becerra, Luke Wang and others.
Kinds of pain that we think we understand

- Acute surgical or post-traumatic pain
- Acute or chronic inflammatory pain
- Pain after peripheral nerve injury
- Pain during childbirth
- Pain due to widespread cancer invading organs.
Features of these “understandable types of pain”

• We can invoke peripheral and spinal mechanisms to explain many of their features.
• We can make animal models that have realistic features.
• These types of pain often respond in predictable ways to analgesic medications.
• Numbing the part of the body where pain is referred generally produces relief.
Features of “Strange” Pain Disorders - 1

• Non-dermatomal patterns
• Difficult to develop realistic animal models
• Inconsistent or negative responses to analgesics
• Inconsistent responses to numbing the area of pain referral
Features of “Strange” Pain Disorders - 2

• Longstanding debates and a confusing literature about roles of psychological factors
• Psychological factors more likely amplify and perpetuate, rather than cause, most of these conditions.
• Strong evidence for effectiveness of treatments that combine psychological and physical rehabilitation
Features of “Strange” Pain Disorders - 3

• Evidence for brain neuroplasticity
• Evidence for functional distortion of the brain’s sensory and motor “maps” of the body
Viewing pain as a distortion of the brain’s map of the body

- Treatment as re-education of use of the body part
- Similarity to rehabilitation after a stroke
- Physical therapy is not just working on the limb, it is working on the brain / the person.
- Mental imagery matters.
Where this lecture will go.

• We will review some of the attached publications on these “strange” pain disorders, and on brain imaging of pain.
• We’ll develop hypotheses regarding how multidisciplinary rehabilitation programs work, and will model a “day 1” talk with a patient and family around “strange” types of pain.
Things we won’t solve during this lecture

• The “hard problem” of consciousness
• An “objective” method of measuring pain or suffering
• Use of fMRI or other brain imaging as a lie-detector test
Strange Features of Phantom Limb Pain

- Severity of pre-amputation pain correlates with likelihood of long-term phantom pain.
- Severity of early postoperative pain correlates with likelihood of long-term phantom pain.
- Intensive regional anesthesia during and after surgery in some studies reduces odds of long-term phantom pain.
Strange Features of Phantom Limb Pain

- Ramachandran et al 1992 - touch of the side of the face evoked sensation and pain referred to the phantom arm.
- fMRI, PET and MEG all show distortion of the homunculus.
- Motor imagery, mirror box therapy, and myoelectric prosthesis all reduce pain and normalize the homunculus.
Strange Features of CRPS

• A minor injury can trigger severe and prolonged pain, extreme allodynia, autonomic changes, movement disorders, and trophic changes.

• The area of pain and dystrophic changes can migrate up or down the limb or to another extremity.

• Intensive rehabilitation can resolve impairment, disability and pain in a majority of subjects.
Strange Features of Fibromyalgia

• Widespread muscle pain without any evident inflammation or injury to muscles. Muscles appear normal by histology and imaging.
• Exaggerated pain to pressure on tender points.
• Occurs without an obvious trigger.
• Many patients also have fatigue, sleep disturbances, and depressed or anxious mood.
• Some patients also have orthostatic intolerance, daily headaches, and other symptoms.
Ways of Watching What the Brain Does During Acute or Chronic Pain

• Structural MRI (especially cortical thickness)
• fMRI
  Blood Oxygen Level Dependent (BOLD) Diffusion Tensor Imaging (DTI)
  Arterial Spin Labeling (ASL)
  Fractional Anisotropy (FA)
• MR spectroscopy
Ways of Watching What the Brain Does During Acute or Chronic Pain

- Position Emission Tomography (PET)
- MEG and EEG
- Near Infrared Spectroscopy (NIRS)

Each method has advantages and limitations.
Effects of Chronic Pain on Brain Structure

• Cortical Thinning in Specific Brain Regions
• What does cortical thinning represent???
  - neuronal cell loss
  - glial cell loss
  - cell shrinkage
  - reduced dendritic volumes
Multiple Chronic Pain Conditions are Associated with Regional Decreases in Gray Matter Volume.

A. Back Pain.    B. Irritable Bowel Syndrome
C. Fibromyalgia   D. Tension Headache
Regional Brain Volumes Normalize if Chronic Pain Resolves: Knee Replacement for Osteoarthritis
Normal Controls Show a Strong Correlation Between Regional Gray Matter Volume and White Matter Fractional Anisotropy. CRPS Patients Show No Correlation.

Fig. 13. Whole-brain relationship between gray and white matter is disrupted in chronic complex regional pain syndrome subjects. Left panel shows that white matter fractional anisotropy (FA; measured for group average skeleton which insures that the tissue examined has 95% probability of being white matter) is correlated to total neocortical volume of the brain (after correcting for age effects). Right panel depicts similar data in complex regional pain syndrome patients, and shows that the relationship is destroyed. In both panels, each symbol represents the brain of a subject: red indicates healthy controls; blue indicates patients. Adapted from [40].
Regional Brain Volumes in Pediatric CRPS
Lebel et al 2011

- Pediatric CRPS patients show loss of cortical thickness in specific sensory and limbic regions during the acutely painful phase.
- Regional cortical thicknesses approach normal after intensive rehabilitation, in less than 3 months of treatment.
Effects of Chronic Pain on Brain Function, Using Psychometric Measures

- Impairment of Normal Information Processing
- Changes in Attention and Reward Systems
- Apkarian “chronic pain is a state of continuous learning without the opportunity for forgetting”
Physiological Correlates of Brain Electrical Activity

Metabolic response:
- ↑ glucose consumption
- ↑ oxygen consumption

Hemodynamic response:
- ↑ blood flow
- ↑ blood volume
- ↑ blood oxygenation

Electrical activity:
- excitatory
- inhibitory
- soma action potential

Electrophysiology:
- EEG
- MEG

Imaging methods:
- FDG PET
- Autoradiography
- H₂¹⁸O PET
- NIRS
- Optical imaging
- fMRI
fMRI
Functional Magnetic Resonance Imaging

- **BOLD signal** - Blood Oxygen-Level Dependent
- Detects local ratio of OxyHgb to DeoxyHgb
- Signal depends on regional blood flow and, secondarily, local metabolic activity.
BOLD Signal Response

“impulse” response to a brief stimulus

more sustained positive BOLD response (larger scale flow changes, excess of HbO2 created, reduction in conc. of Hbr)

post-stimulus undershoot, return to normal flow but slow CBV recovery (giving effective increase in [Hbr])

brief initial “dip” (HbO2 → Hbr, local flow changes)

fMRI “dip”: Menon et al., MRM 33:453; Ernst & Hennig, MRM 32:146; Hu et al., MRM 37:877
fMRI Additions

- headphones
- prism glasses
- video screen
- button response box
- video projector
- stimulus control computer
- gating
fMRI / BOLD: Experimental Paradigms

• Like a difference spectrum – multiple repeated cycles of stimulus on versus stimulus off
• Very small signal, requires multiple runs to get signal to noise ratio
Functional MRI

- need many samples of the brain
- need fast imaging capabilities
  - e.g. echo planar imaging
  - fast gradient coil
  - big disk!
Head Motion Correction

- Chen/Pelizzari surface based approach
Volume Rendering

axial

sagittal

coronal

Hierarchical language task
CBF and CMRO$_2$ Coupling

- **Historical Perspective**
  - Roy and Sherrington, 1890: proposed coupling of CBF and metabolism
  - Coupling confirmed in resting brain 1970s–1980s. Almost all neuronal energy derives from oxidative glucose metabolism
Inter Subject Comparison

- Talairach normalisation

J. Talairach and P. Tournoux

Drury et al.
fMRI / BOLD:
Advantages

• Excellent **spatial** resolution – can see changes in very small structures
• Can see activity in deep brain structures (unlike EEG-based methods)
• No radiation exposure (unlike PET)
fMRI / BOLD: Disadvantages

- Mediocre temporal resolution
- Repeated on-off stimuli is artificial, and can be influenced by habituation, sensitization, or attention.
- Expensive
- Requires cooperation and immobility
- Difficult to study real-world movement.
fMRI / BOLD:
What is being measured?

• Intensity of perception more than intensity of stimulus: posterior insula

• Anticipation of pain, rather than pain itself: nucleus accumbens and amygdala show activations before the stimulus.
Acute Experimental Pain in Healthy Subjects: Correlation Between Stimulus Intensity and Pain Reports
BOLD Signal in Posterior Insula Tracks Well with Perceived Pain Intensity.
BOLD Signal in Posterior Insula Tracks Well with Perceived Pain Intensity.
ASL
Arterial Spin Labeling

• MRI technique used to measure regional blood flow
• No isotopes, gadolinium or radiation are required.
PET
Position-Emission Tomography

• Detects gamma ray emission from positron-label, computer reconstruction of a map, analogous to CT-scans

• $^{18}$F 2-deoxy glucose – FDG – marker for glucose utilization
PET
Position-Emission Tomography

• Detects gamma ray emission from positron-label, computer reconstruction of a map, analogous to CT-scans

• $^{18}$F 2-deoxy glucose – FDG – marker for glucose utilization

• Often combined with regular CT or MR to link to anatomy
PRIMARY SOMATOSENSORY CORTEX ACTIVATED BY BOTH PAINFUL AND INNOCUOUS STIMULATION

PAIN VS CONTROL

VIBRATION VS CONTROL

DV +56

DV +57

AP -31

AP -31

T-VALUE

5.9

3.5
PET
Advantages

• High signal to noise – avoid need for difference spectrum/subtraction like fMRI
• Doesn’t require repeated on-off stimuli
• Functional ligands available that assess glucose, dopamine, and serotonin
PET

Disadvantages

- Expense, short-lived isotopes made in a cyclotron, requires timing of preparation just before scans.
- Radiation exposure – PET alone may be 5 – 7 mSV; when combined with CT may be around 23-26 mSV.
- Mediocre spatial resolution
NIRS
Near Infrared Spectroscopy

• George Hoffman’s SPA lecture from 2011 is the Gold Standard; read this for details.
• Relationship to regional oxygenation
• Contributions to the signal
• Published studies of infant cortical responses to heelsticks. (Slater et al, Anand et al)
NIRS
Near Infrared Spectroscopy

• Advantages: no radiation, mobile, rapid response time
• Disadvantages: poor spatial resolution, can’t see deep brain structures involved in affective responses to pain
EEG
Electroencephalography

• Advantages: no radiation, mobile, rapid response time
• Disadvantages: can’t see deep brain structures involved in affective responses to pain, influence of drugs on background activity
• Unique use: pain-evoked responses in neonates (Fitzgerald’s group)
MEG
Magnetoencephalography

• Neurons generate electric currents.
• Moving electric charges produce small magnetic fields (Faraday, Maxwell, ....).
• Magnetic fields over the brain’s surface are very small, requiring fancy technology to shield from random nearby magnetic fields.
MEG
Magnetoencephalography

- The “inverse problem”: how to use the observed magnetic and electrical signals to calculate the precise location of the source of the signals.
- The solutions of these equations are not unique – different sources could generate a similar field pattern.
MEG
Advantages

• The measured quantity is related to electrical activity per se, not just to blood volume or blood flow.
• Excellent temporal resolution (milliseconds)
• No radiation exposure
• Patients’ heads are constrained, but they can move their limbs in a study paradigm.
MEG
Disadvantages

• Poor spatial resolution
• Detects activity near the brain surface, not in deeper structures (i.e. “emotional” cortex)
Effects of Chronic Pain on Brain Function, Using Imaging and Electrophysiology

- Designs are complicated.
- One-sided pain: ipsilateral vs. contralateral
- Comparison to healthy non-painful controls.
- Pre- vs. post resolution of chronic pain: adults undergoing hip or knee arthroplasties.
Effects of Chronic Pain on Brain Function, Using Imaging and Electrophysiology

- Changes in regional activation, at rest and with stimuli
- Distortions of the brain’s sensory and motor “maps”
People with Chronic Pain Have Distorted Sensory and Motor Imagery

• Ramachandran et al  Science 1992; 258: 1159-60

• Bray and Moseley  Brit J. Sports Med. 2011; 45 168-73
Activity in Insula and Median Prefrontal Cortex Correlates with Spontaneous Fluctuations in Pain Intensity in People with Chronic Low Back Pain.

**Fig. 5.** Brain activity for rating spontaneous fluctuations of back pain in chronic back pain patients show a strong correlation with intensity and duration of the condition across all participating patients. The observed correlations are strong enough that we can assert that the task can be used to predict intensity and duration of chronic back pain in individual subjects within an error of 20%. Figure adapted from [8].
Figure 3 Brain activations (fMRI) during non-painful mechanical stimulation of the healthy side (a) and the hyperalgetic complex regional pain syndrome-affected side (b). Higher activation of secondary somatosensory cortices (S2), middle frontal cortices and the posterior part of the anterior cingulate cortex during mechanical hyperalgesia (b) (modified after [28]).
Normal Subjects with Experimental Thermal Pain and Patients With Chronic Pain Show Similar Activations in Sensory Regions, Different Activations in Limbic Regions.

Fig. 6A. Brain activity patterns for various clinical chronic pain conditions. Activity maps: are group-averaged responses for different pain conditions. Activity maps: Thermal pain, knee-pressure-induced pain in healthy subjects, and in osteoarthritis patients (OA) show similar patterns of brain activity, implying that all results correspond to acute pain activity. In contrast, brain activity for spontaneous pain in different clinical conditions (chronic back pain [CBP], osteoarthritis [OA], pelvic pain [CPPS], and PHN, post-herpetic neuralgia [PHN]) show different activity patterns, engaging to different extents sensory and limbic brain areas. In PHN, tactile allodynia and spontaneous pain evoke relatively distinct brain regions too. Bar graphs: Magnitude of activity in 2 limbic regions (MPFC and Amygdala) and 2 sensory regions (thalamus and insula) are compared for 4 groups: healthy subjects for thermal pain, Healthy th; chronic back pain patients for spontaneous pain, CBP sp; post-herpetic neuralgia for spontaneous pain, PHN sp, and for tactile allodynia, PHN al). Thermal pain and PHN alldynia show larger activity in the sensory regions, while spontaneous pain in CBP and PHN evoke more limbic activity.
**Fig. 6B.** Brain activity in medial prefrontal cortex (mPFC) shows high specificity for chronic back pain. Magnitude of mPFC regional activity (as identified in chronic back pain patients) across 5 groups of subjects. Each symbol represents an individual subject. The threshold indicated by broken green line distinguishes chronic back pain (CBP) from pelvic pain (CPPS), osteoarthritis (OA), post-herpetic neuralgia (PHN) for spontaneous pain, and healthy subjects for acute pain (healthy) at an accuracy greater than 90%. The number of subjects studied in each group is indicated above.
Fig. 9. Distinct functional connectivity between nucleus accumbens and the rest of the brain are observed in chronic pain patients in contrast to healthy subjects. This shift in connectivity is tightly correlated to the magnitude of back pain reported by the patients. (A) Healthy: Functional connectivity between nucleus accumbens and the rest of the brain in healthy subjects. We observe extensive bilateral insula involvement. (A) CBP: Functional connectivity for nucleus accumbens in chronic back pain patients. Functional connectivity is shifted away from the insula to medial prefrontal cortex. (B) Strength of connectivity between nucleus accumbens and medial prefrontal cortex in relation to the magnitude of back pain reported. Each red symbol is an individual chronic back pain patient; blue circles are healthy controls. The higher the magnitude of spontaneous pain of back pain the stronger is the correlation between mPFC and NAc, implying more information sharing between these 2 brain regions. Figure adapted from [11].
Brain fMRI of children with RSD/CRPS with Drs. Lebel, Borsook, Becerra et al. Brain 2008

Brush A - U

Cold A - U

Insula

Anterior Cingulate

Amygdala

Hypothalamus
Figure 2 Cortical reorganization in complex regional pain syndrome (CRPS). In this case, the left hand was affected. (a) The cortical extension of the hand (distance between the first and fifth finger, D1 and D5) was in the acute stage decreased from 1.42 cm in the healthy side to 0.8 cm in the affected side. Somatotopic alterations correlated with the painfulness of the disease. (b) Normalization of the somatotopy in the gyrus post-centralis 1 year after successful therapy (modified after [77]).
Adults with CRPS Show Impaired Activation of Descending Pain Inhibitory Systems.

- Seifert, Maihofer et al. Brain 2008; 132:788-800
- Experimental repetitive electrical pain stimuli to affected and unaffected limbs to activate descending pain inhibitory responses.
- Reduced inhibitory responses from either side compared to controls.
Cortical Representation in CRPS

• Maihofer et al. Neurology 2006; 66:711-17 - get ref.

• For patients with CRPS of the hand, there was a smaller volume of representation in primary sensory cortex (S1), compared to controls.
Multidisciplinary Rehabilitation Can Improve Impairment, Disability and Pain, and Can Normalize Aspects of Brain Imaging

- Which components?
- How does it work?
CRPS

• Pediatric: Lebel et al, 2010, 2011 – before and after 3 week day-hospital PT, OT, CBT

• Adults: Mirror-box (Moseley et al)
Figure 8: (A) Cold Affected limb - CRPS$^+$ vs. CRPS$^-$; (B) Cold Unaffected limb CRPS$^+$ vs. CRPS$^-$
Phantom Pain

• Myoelectric prostheses
  Lotze et al Nature Neurosci. 1999
• Mirror-box therapy
  Diers et al Pain 2010; 149: 296-304
• Immersive virtual reality
• All of these interventions seem to reduce disability, reduce pain, and normalize patterns of regional brain activation and homuncular organization.
What about patients with “psychiatrically-based” pain?

• Malingering, lying or factitious disorders
• Somatization, somatoform disorders
• Conversion disorders
• “Hysterical” anesthesia or paralysis
Nondermatomal Sensory Deficits

- Mailis-Gagnon et al  Neurology 2003
- Patients with an apparently insensate arm or leg, with spontaneous pain.
- Intact NCV, EMG, brain and spine imaging, and SSEPs.
Patients with “Hysterical Anesthesia” show reduced activation of thalamus, S1, and insula.

Figure 1. Regions of activation related to the brush stimuli applied to the control limb (A, brush perceived condition) and to the affected limb (B, brush unperceived condition). Arrows in brain images show the key areas of activation. Images are displayed so that the hemisphere contralateral to side of the body stimulated is indicated by the “c” and shown on the right. Significance is indicated by the z-score color bar.
Clinical Case

- A 13 year old girl comes for a first Pain Clinic appointment.
- History of 2 years of constant daily 10/10 pain in widespread locations in the upper and lower body.
- Sleep is disturbed, there is daytime fatigue, and she has not been in school for the past year.
Clinical Case

• Previous consultations and laboratory tests have been extensive, and unrevealing.
• No features of your thorough HPI, PMH, or ROS suggest a specific systemic illness.
• She also has chronic daily headaches and orthostatic intolerance.
• She is taking 5 medications for pain.
Physical Exam

• Oriented, conversant, calm
• Affect could either be sad, anxious, or happy – any of these can coexist with the above presentation.
• No focal neurologic deficits.
• Tenderness includes ACR tender points for fibromyalgia, but also includes many other areas of muscles and tendons.
Questions – Part 1

• What is your diagnostic impression?
• What interventions have evidence of helping this child and family?
• What factors influence this child’s prognosis?
• How can you get the child and family to buy in to your impressions and recommendations?
Questions – Part 2

• What lessons from the last 80+ slides can help in this discussion?
• A role-playing session will follow.
Conclusions

• Brain imaging and electrophysiologic mapping are providing interesting observations about how the brain changes structurally and functionally with acute and chronic pain.

• This field is in its infancy, and conclusions from small studies should be circumspect.
Conclusions

• Some of these plastic structural and functional changes can be reversed by treatments that actively engage the person in physical and psychological rehabilitation.

• There may be ways in the future to improve upon rehabilitative approaches that “retrain the brain”.