Central Neural Actions of Acupuncture, Insights from Brain Imaging

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Temporal Dynamics of Acupuncture

- Acupuncture analgesic effect (VAS of chronic low back pain) is maximal several hours to 2 days after treatment.

- What are the dynamic mechanisms involved in acupuncture effects?

Price et al., 1984
Model of Temporal Action of Acupuncture (and Sham Acupuncture)

- **Acute Effects**

  - Treatment 1
    - Insertion
    - Manipulation
    - Retention
  - Multiple Treatments Over Weeks/Months
    - "Build-Up" of Effects
      - Acute Effects Overlaid on Sustained Effects
  - Treatment X
    - Insertion
    - Manipulation
    - Retention
Acupuncture Needle Manipulation Deactivates Limbic System

Subsequent work then shows that this deactivation is during *De Qi* only and is not seen during pain.
The Type of Needle Manipulation Affect Brain Response: Manual versus Electrical

Greater activations with electroacu, also somewhat different regions.

Napadow et al HumBrainMapping 2005
What happens immediately following stimulation?

Acute Effects

“Build-Up” of Effects

Multiple Treatments Over Weeks/Months

Immediate Following Treatment

Acute Effects Overlaid on Sustained Effects

Treatment X

Insertion
Manipulation
Retention

Treatment 1
Insertion
Manipulation
Retention
Does Acupuncture Affect *Resting* Brain Activity After Stimulation?

- N=15 healthy adult subjects
- Rest fMRI $\rightarrow$ cross hair (+) fixation for 5.5 minutes
- Siemens Trio 3T, 12-channel coil (TR/TE = 3sec / 40msec, coronal slices, whole brain coverage, 3.13 x 3.13 x 3.6mm)
- Use Independent Component Analysis (ICA) to find distinct known networks (default mode network [DMN]) in resting fMRI data

**fMRI SCANNING PARADIGM**

<table>
<thead>
<tr>
<th>REST 1</th>
<th>SHAM</th>
<th>REST 2</th>
<th>STRUCTURALS AND FIELD MAPS</th>
<th>REST 3</th>
<th>ACUP</th>
<th>REST 4</th>
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<tbody>
<tr>
<td>5.5 minutes</td>
<td>5.5 minutes</td>
<td>5.5 minutes</td>
<td>&gt;15 minutes</td>
<td>5.5 minutes</td>
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compare post vs. pre  
compare post vs. pre
Acupuncture Increases Extent of Resting DMN Connectivity [Post-Acu – Pre-Acu]

Brainstem Regions

- Increased DMN connectivity with pain and anti-nociceptive related brain regions post-ACUP: periaqueductal gray (PAG) and substantia nigra (SN)

Dhond et al, Pain 2008
Acupuncture Increases Extent of Resting DMN Connectivity

Cortical and Subcortical Regions

Dhond et al, Pain 2008
Acupuncture (not Sham) Increases Resting DMN Connectivity

• Acupuncture increases spatial extent of resting connectivity between DMN and:

  • **limbic pain and anti-nociceptive** - ACC, PAG
  
  • **affective** - amygdala, ACC
  
  • **memory** - hippocampal formation, MTG

• **NO regions demonstrated greater connectivity pre-** compared to post-acupuncture
What happens during a long course of treatment?

Multiple Treatments Over Weeks/Months

“Build-Up” of Effects

Acute Effects

Treatment 1
  - Insertion
  - Manipulation
  - Retention

Treatment X
  - Insertion
  - Manipulation
  - Retention

Acute Effects Overlaid on Sustained Effects
Acupuncture (and Sham) Effects on Chronic Pain Accumulate and Persist Over Time

Tension Headache

Fig 2  Mean (95% confidence interval) number of days with headache. Patients in the waiting list group received acupuncture after week 12 (dotted bars)

Melchart et al. BMJ 2006
Figure A: Comparison between Healthy Control, CTS Baseline, and CTS Post Acup treatments. Highlighted regions include PreCG and SI.

Figure B: Healthy Control, CTS Baseline, and CTS Post Acup treatments with marked points 2, 3, and 5.

Napadow et al., NeuroImage 2007
Napadow et al., HBM 2006
Opioid Receptors and Acupuncture

- Opioid receptors belong to the G protein-coupled receptor super-family.
- They are located in “pain” neuropathways.
- Opioid receptors increase neuronal inhibition.
  - Reducing calcium influx: presynaptic.
  - Increasing potassium efflux: postsynaptic.
- μ-opioid receptors (MORs) bind endogenous and exogenous opioids.
  - $^{11}$C-carfentanil: Positron Emission Tomography (PET).

Chaturvedi et al. *Biopolymers* 2000
Receptor Availability

PET Measurements

Tracer Transport (rCBF x Tracer Extraction)

Incorporation to Specific Binding Sites

1 min 2 min 3 min 5 min 10 min 30 min 70 min

Data Analysis

Generation of Parametric Maps
Logan Plots (DVR)

Coregistration with Anatomical MRI

Non-Linear Anatomical Standardization (ICBM Template Space)

Statistic Images for Statistical Parametric Mapping (SPM)
Occupancy and number of μ-opioid receptors influences BP.

Increased Release of Endogenous Opioids

Acupuncture PET Trial in FM

- 20 FM patients (all female) randomized to Acupuncture (TA; n=10; 46.3yrs.) or Sham Acupuncture (SA; n=10; 42.3yrs.; p-value=0.53)
- 9 treatments over the course of 4 weeks
- First and last treatment occur during PET imaging

Harris et al. Neuroimage 2009
Acupuncture increases MOR BP whereas sham decreases or has no effect.
Increase in MOR BP following acupuncture are associated with less pain.

Harris et al. Neuroimage 2009
Is there any change in acute effects over time?

Acute Effects

Treatment 1
- Insertion
- Manipulation
- Retention

Multiple Treatments Over Weeks/Months
- "Build-Up" of Effects

Acute Effects Overlaid on Sustained Effects

Treatment X
- Insertion
- Manipulation
- Retention
Acupuncture has specific effects during needle retention (acute effect)

True acupuncture increases MOR BP immediately following needle insertion and manipulation. This effect is seen during needle retention. This is not observed with sham acupuncture.

Harris et al. Neuroimage 2009
Differential Immediate Effects of Acupuncture and Sham Following Long-Term Therapy

Amygdala/Striatum

Temporal Pole

all p<0.05 corrected
Mechanisms...

- Deactivation of limbic system neural activity potentially an autonomic nervous system response.
- Increased neural connectivity between pain modulatory brain region such as the PAG and other networks.
- Increased numbers of receptors over time.
- Long-term synaptic plasticity LTP and LTD are modulated by acupuncture.
What if Mechanisms of Acupuncture and Sham are Different?

- Implications for clinical trials: specific effects of needling are not additive with placebo effects. Would a pathway analysis make more sense?
- Synergistic effects of acupuncture with other interventions.
  - Exogenous opiates administered following a course of acupuncture may be more effective. (Reduction in post surgical opiate use. Kotani et al. *Anesthesiology* 2001.)
- Acupuncture is not a sham.
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Thank You for Listening