Quantitative fMRI of Acupuncture Induced Brain Activity

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The traditional Chinese medicine suggested that energy travels through the body by certain energy channels or circuits, known as meridians or nadis.

If there are blocks in these energy channels, or imbalances of any sort, the result manifests itself as disease in one form or another.

Through the specific acupoint placement of needles those channels can be unblocked to induce the natural state of good health coming back.

Despite of many unclear mechanism from scientific point of view, acupuncture is becoming an increasingly popular method of alternative medicine on pain relief in worldwide.
Chronic pain is a complex experience and is particularly clinically challenging in patients with many kinds of cancer or post-operation.

In 1999, IASP emphasized that pain should be considered as a new important sign and physiological parameter.

In 2004, IASP declared an annual second Monday in October as Global Day Against Pain.

pain is always subjective: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."

"an inherent quality of life that appears early in development and serves as a signal for tissue damage."

- The International Association for the Study of Pain (IASP)
In last 40 years, studies have shown that there are pain related opiates receptors in brain.

Candace Pert discovered that the brain has its own receptors for opiates. This provides evidence that the brain must produce something, on its own, that is akin to drugs like morphine.

Based on the animal experiments, Han jisheng discovered the principle of eAcupuncture to treat pain.
Acupuncture induced analgesia
Human Observation:

Pain threshold changes significantly with acupuncture.

Han jisheng et.al, “the affection of pain threshold by acupuncture stimulation”. Jourial of Chinseese Medicine, 1973, Vol.3:151
Rabbit experiment: cross infusion of CSF

Extracted the CSF (Cerebrospinal fluid) from the donor rabbit that have been applied the acupuncture, and infused it into the ventricle of recipient rabbit.

The change of tail flick latency demonstrated that there was a significant rise in pain threshold for both rabbits, revealing there existed a neurochemical basis in the brain of rabbit.
EAcupuncture induced neurotransmitters release with different frequency

![Graph showing neurotransmitter release with different frequencies of EA]

- **2Hz EA** increase Enk release
- **100Hz EA** increases Dyn release


At low frequency electroacupuncture the analgesic effect was dominated by metenkephalin while at high frequency by dynorphin
Efficacy for Specific Disorders
- postoperative and chemotherapy nausea
- dental pain vomiting and the nausea of pregnancy

The Biological Effects of Acupuncture
- could increase opiate release,
- also affect the function of immunity and blood stream

Response Rate
- majority responding, minority not responding

With less side and adverse effects, insurance companies in U.S now provide coverage for acupuncture services.
What happens in the brain and how to understand the release of endogenous opioids during acupuncture treatment?

And how to estimate the activated or deactivated brain nucleus with corresponding nerve fiber while electroacupuncture specific the pain control points?
Conceptual relationship of therapeutic acupuncture, functional MRI, and the role of the brain

Evidences of pain related brain region

By using electrophysiological assessment and functional brain MRI, Studies have shown that specific pain-related brain regions can be activated while acupuncturing appropriate acupoints.

Wei-Ting Zhang , Zhen Jin , Ji-sheng Han, et al. Relations between brain network activation and analgesic effect induced by low vs. high frequency electrical acupoint stimulation in different subjects: a functional magnetic resonance imaging study. Brain Research 982 (2003): 168–178
Quantitative fMRI

BOLD signal that dominates by venuoles and vein reflects indirectly the neural activities with a qualitative way.

Brain perfusion estimates quantitative cerebral blood flow (CBF), providing a more strong association with the regional neural activities.


Comparing with perfusion by ASL, baseline drift effects of BOLD result in poor sensitivity for detecting slow variations in neural activity.
ASL is a technique developed for the measuring of local tissue perfusion with MRI that is completely non-invasive and provides relatively high spatial and temporal resolution as compared to many other current functional imaging techniques.
By using corrected ASL and CSF images, ASL gives direct measurements of CBF to a local brain voxel in an imaged slice of interest.
Dual Echo Spiral Sequence

1st Echo
- CBF-weighted
- QUIPSSII, PICORE
- 800 msec labeling duration (prepti1)
- 700 msec post-label delay (prepti-prepti1)
- 3.0 sec TR (7/15 sec effective TR)
- Spiral readout
- 3.1 msec TE

2nd Echo
- Spiral readout
- 30 msec TE
- BOLD-weighted
Experiment Design

Heku (合谷) and Laogong (劳宫) acupoints on left hand stimulated at 100 Hz with MRI-compatible device. The current ranges from 6~8 mA based on the individual pain tolerance.

Left hand finger tapping

electrical acupuncture

Hans 200 electroacupuncture device (Nanjing Gensun Medical Technology Co. Ltd., Nanjing, China) utilizes MRI-compatible electrodes to enable simultaneous fMRI and electroacupuncture

- Fat Saturation
- Slicethick = 8mm,
- slicegap = 2mm
- Number of Slices: 10~12
Electro-Acupuncture Experiments

(March 3 – September 28)

Georgia Tech student Christopher Glielmi working with students Zhang Beiru, Zhang Yue and Guo Jia to devise fMRI protocol at Peking University First Hospital

Pain tolerance measurement before applying electro-acupuncture

So far, 137 Electro-Acupuncture fMRI experiments were carried out at Peking University First Hospital with GE Signa EXCITE 3.0T MR Scanner.
Data Analysis

Apply statistical test comparing each voxel’s image intensity fluctuation in time to experimental blocks

Regions statistically correlated with acupuncture application are considered “activated”

BOLD and ASL signals in finger tapping tasks. The figure on the left shows the raw image and the figure on the right shows the timecourses of a 3 by 3 region centered at the crosshair on the left.
Activation in right post-central sulcus, relating to primary sensory cortex (S1) contralateral to electroacupuncture stimulation.
BOLD based activation

- Insula
- Thalamus

CBF based activation

- caudate head
- Thalamus

smoothing, $p<5 \times 10^{-2}$, extent $> 20$ voxels
Both BOLD and CBF demonstrate activation similar to previous results including activation in SII, insula, thalamus.

Activation in secondary somatosensory cortex (SII) and insula, which relates to pain processing

Subcortical activation in thalamus appears better localized with CBF than BOLD
BOLD based deactivation

- anterior cingulate (前扣带回)
- medial frontal gyrus (额内侧回)

CBF based deactivation

- parahippocampal gyrus (海马旁回)
- Culmen (小脑山顶)

smoothing, $p<5\times 10^{-2}$, extent $> 20$ voxels
Consistent with previous findings, deactivation (decreases in BOLD CBF signal) in hippocampus (HC) for BOLD and parahippocampal gyrus (pHC) for CBF.

BOLD also demonstrates deactivation near default mode regions medial frontal gyrus (MFG) and posterior cingulate cortex (PCC).
Accomplishments To Date

Implementation of ASL protocol to yield reliable CBF during electroacupuncture

Sufficient sensitivity for both cortical and subcortical regions related to sensory and limbic systems

Robust BOLD and CBF mapping of brain activity during anesthesia.

A strong foundation for reproducibility studies comparing BOLD and CBF contrasts
Plan for the future

- A novel KCL pain measurement system
- Experiment with Prof. Jisheng Han

- Publication of preliminary data
- Investigation of reproducibility
- Trace fiber tracts within brain and connectivity while acupuncture
- Study neurofeedback during acupuncture.

Diffusion Tension Imaging Sample from people.csail.mit.edu/lauren/dtmri.html
Collaborated with the group leaded by Dr. Han and discuss electroacupuncture specifics, 2008

Georgia Tech student Christopher Glielmi working with students Zhang Yue, Wangjing, Guojia, Zheng dandan and Zhang Beiru to devise fMRI protocol at Peking University 2008

Drs. Zhang, Hu and Fan meet at the Biomedical Imaging Technology Center at Emory University, 2007

Collaborated with the group leaded by Dr. Han and discuss electroacupuncture specifics, 2008
Acknowledgements

This work was supported by the Georgia Tech/Emory University-Peking University Biomedical Engineering collaborative seed grant.

Thanks!
## The activation results

**SCAN A: BOLD**

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The threshold for P:  $P(\text{correct}) < 0.05$ Nearest Gray matter
## The activation results

**SCAN B: CBF**

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The threshold for P: P(correct)<0.05 Nearest Gray matter
The deactivation results

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The threshold for P: P(correct)<0.05 Nearest Gray matter
The deactivation results

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The threshold for P: P(correct)<0.05 Nearest Gray matter