Dynamic response of the human brain to acupuncture at LV3 as monitored by fMRI: evidence of limbic system modulation

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INTRODUCTION

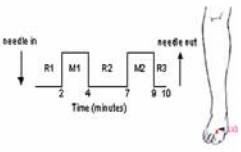
Understanding the neural substrates of acupuncture, especially the effects on the human brain will promote its development into evidence-based medicine. Acupuncture is used to treat diverse disorders, and acupuncture at a single acupoint can affect multiple physiological and functions. We postulate that the limbic system which plays a central role in the regulation and integration of multiple brain functions may constitute an important pathway of acupuncture action. We monitored the dynamic response of the human brain during acupuncture at several classical acupoints that are known for their strong analgesic and diverse modulatory effects. Studies at LI4 and ST36 provided evidence in support of the hypothesis[1,2]. This report presents the findings of acupuncture at LV3 on the foot.

METHODS

Subjects: 51 right handed subjects acupuncture-naïve volunteers, age 20-47 y.o. (mean 29, SE 0.41), 36 F/20 M. 47 subjects received acupuncture and 17 received sensory stimulation. The datasets of 4 subjects were excluded in fMRI data analyses due to excess motion.

Acupuncture: Bidirectional needle rotation with even motion, 60/min, for 2 periods of 2 min each (M1 and M2), was performed at LV3 on the right during fMRI (Figure 1). Scanning commenced with R1 and ended with R3 (10 min runs), with needle in place during rest. Duplicate runs were performed.

Fig 1



The subject was questioned after each run about sensations experienced during stimulation and rated the intensity of each sensation on a scale of 0-10.

Control: Tactile stimulation over acupoint with von Frey monofilament and a matched paradigm.

fMRI: 1.5T Siemens Sonata with EPI; whole brain scan, 3mm sagittal slices, 20% gap; T2*- weighted sequence (TE 30 ms, TR 4s, matrix 64 x 64, FOV 200 mm, flip angle 90º, in-plane resolution 3.125 X 3.125 mm); 3D T1-weighted sequence for high-resolution structural images.

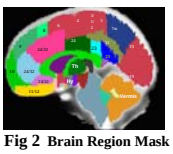


Fig 2 Brain Region Mask

Data analysis employed AFNI. An anatomical mask was created using the MNI305 brain[3] as template (Fig 2). The anatomically parcellated structures of interest were associated with Brodmann's areas to facilitate functional anatomical correspondence according to fMRI literature. The hemodynamic response based on the extent and the % change in signal intensity within each structure and normalized to the structure volume was calculated by automated analysis.

RESULTS

Psychophysical Response: In acupuncture, 41 subjects experienced *deqi* and 16 experienced *deqi* mixed with sharp pain. In tactile stimulation, 8 reported and 13 did not report *deqi* sensations.

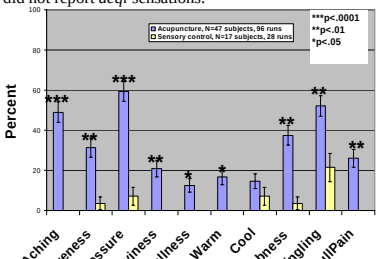


Fig 2 Deqi Sensations: Acupuncture *deqi* vs Control:

Aching, soreness, pressure, heaviness, numbness and dull pain were common in acupuncture, rare or absent in sensory control. The most common sensation in control was tingling.

Funding: NIH, NCCAM 1P01-AT002048_01, R21-AT00978
National Center for Research Resources
MIND Institute

Hemodynamic Response :

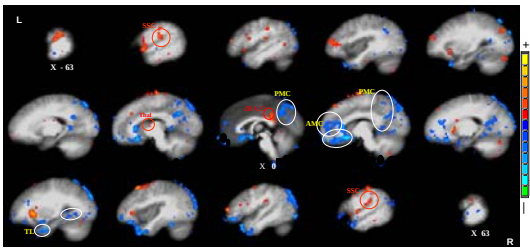
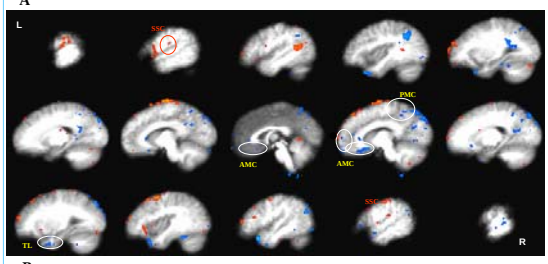


Fig 4 Acupuncture *Deqi* 53 runs/37 subjects, p< 0.0001
Whole brain sagittal sections showing clusters of deactivated regions in the limbic-paralimbic-neocortical network: posterior medial cortex (PMC), anterior medial cortex (AMC) and temporal lobe (TL). Signal decreases were bilateral, with predominance on the right (ipsilateral). **Activation** was more limited, occurring in the somatosensory cortex (SSC), thalamus (Thal) and posterior cingulate (dorsal BA23).

A



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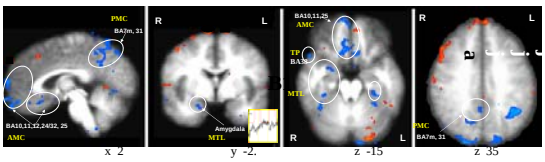
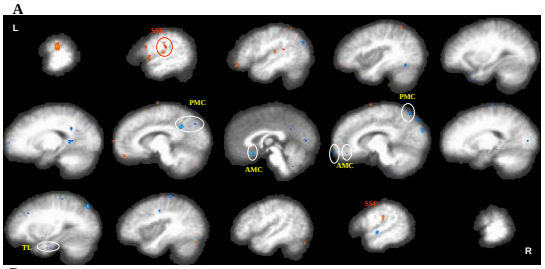


Fig 5 A,B Acupuncture *Deqi* 26 runs/17 subjects, randomly matched with Sensory Control (Fig 5A,B), p< 0.0001

Deactivated regions in the AMC (BA10, 11, 12, pregenual and subgenual cingulate BA24/32, SG25), PMC (precuneus BA7m, cingulate BA31), temporal lobe (amygdala, parahippocampus, temporal pole) Deactivation was bilateral, with predominance on right.

A



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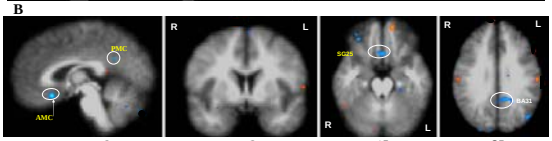


Fig 6 A.B. Sensory Control 26 runs/17 subjects randomly matched with Sensory Control p <0.0001
The hemodynamic response was very limited compared with Acupuncture *Deqi* (See Fig 5). Focal signal deactivation was seen in AMC (SG25) and PMC (BA31).

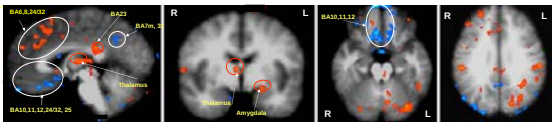
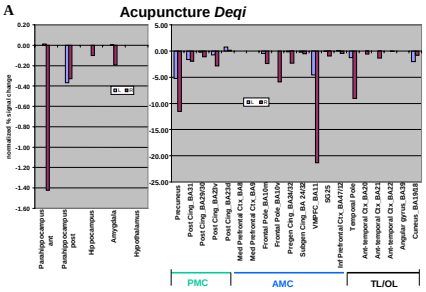


Fig 7: Acupuncture *Deqi*+ sharp pain 21 runs/15 subjects p<0.0001
The deactivation of AMC, PMC seen in *deqi* (See Fig 5) was significantly reduced. Activation became more prominent, appearing in the dorso-medial prefrontal cortex, the middle and posterior cingulate and the amygdala

A



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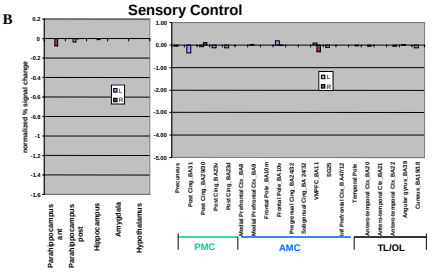

Fig 8 BOLD response of structures defined by region mask
A: Acupuncture *deqi* - (Fig 4 data) **B: Sensory Control -** (Fig 6 data)

Acupuncture *deqi* elicited significantly more extensive deactivation than sensory control. The % signal change (normalized to structure volume) was most prominent in the parahipppocampus, precuneus, frontal pole and the ventromedial-prefrontal cortex (VMPFC). The response was bilateral, with predominance on the right (Fig A). Deactivation of the sensory control was restricted to focal signal decreases in the posterior cingulate, VMPFC and parahippocampus (Fig B).

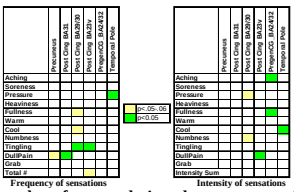

Fig 9. p values for correlations between sensations and BOLD response of brain structures (in right hemisphere).
(The more frequent or the more intense the *deqi* sensation, the greater the decrease in BOLD signals.)
The deactivation of the precuneus and several divisions of the posterior cingulate in the PMC correlated with the frequency and intensity of dull pain. The pregenual cingulate correlated with the intensity of aching and fullness. The temporal lobe correlated with pressure (frequency) and cool sensation (intensity).

DISCUSSION and CONCLUSIONS:

Acupuncture at LV3 produced extensive deactivation of the limbic-paralimbic-neocortical network with *deqi*. The response was attenuated in the concomitant presence of pain. The general pattern concurs with results reported for acupoints LI4 and ST36[1,2], although with variations in extent and magnitude of signal change and preferential localizations between the acupoints. Further analysis to compare the central effects of the different acupoints is in progress. Most of the brain regions involved are known to be activated by pain, anxiety and psychostimulants[4-8]. The deactivation seen with *deqi* suggests that acupuncture can counter the deleterious effects of noxious stimuli and help restore the normal balance of neurophysiological functions. The predominance of limbic network deactivation on the right (ipsilateral) hemisphere contrasts with the predominance of the somato-sensory cortex (SSC) activation on the left. Whether the lateralization of deactivation to the right hemisphere is dependent on the the side of the acupuncture stimulation or not warrants follow-up investigation. The correlations between the *deqi* sensations and the BOLD response of brain structures are preliminary findings that require further analysis and perhaps a study of larger sample size for validation. Acupuncture may modulate the activity of intrinsic functional networks that respond to changes in internal milieu and external environments[9]. The limbic system, which plays a central role in the regulation and integration of multiple brain functions, may constitute an important pathway of acupuncture action

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