

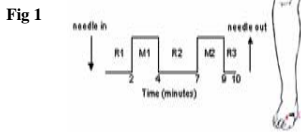
### INTRODUCTION

The unique sensory response to acupuncture, termed *deqi*, is important to the therapeutic outcome according to traditional Chinese medicine. The response may be occasionally mixed with inadvertent sharp pain. The neuroimaging literature shows discrepancy as to whether acupuncture activates or deactivates the pain neuromatrix (1-4). Prior fMRI studies from our group demonstrated that the central effects were distinct between *deqi* and noxious pain. Acupuncture *deqi* absent sharp pain at L14 and ST36 deactivated the cortico-limbic system, including most structures of the pain neuromatrix (1,2). Here we present additional evidence from another classical acupoint Taichong (LV3) on the foot that is commonly used for reducing pain and other modulatory effects.

### METHODS

**Subjects:** 51 right handed, acupuncture-naïve, 20-47 year old (mean 29, SE 0.41), 36 F/20 M healthy subjects. 47 of the participants 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 with fMRI monitoring (Figure 1). Scanning commenced with R1 and ended with R3 (10 min run), with the needle remaining in place during rest. Duplicated runs were performed for most of procedures.



After each run the subject was asked to score the intensity of *deqi* sensations and sharp pain experienced during acupuncture or sensory stimulation on a scale of 0-10 (0 = no such sensation, 10 = unbearable, strongest intensity imaginable).

**Control:** Tactile stimulation over acupoint with 5.88 mm 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 90°, in-plane resolution 3.125 X 3.125 mm); 3D T1-weighted sequence for high-resolution structural images.

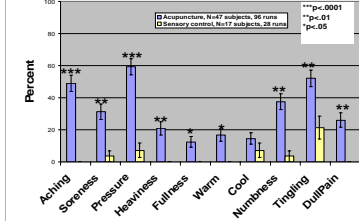
**Data analysis:** AFNI was employed. Statistical parametric mapping was completed with generalized linear modeling. The statistics were mapped onto the subject's own high resolution 3D anatomical dataset in Talairach space. Data were thresholded at  $p < 0.003$  for single subject, and  $p < 0.001$  for group average data, with a minimal cluster size of 3 contiguous voxels. One way ANOVA was used for comparison among acupuncture *deqi*, acupuncture *deqi* mixed with sharp pain (Mixed) and tactile stimulation. Cross-correlation analysis (CCA) was performed for detecting the functional connectivity between the pregenual cingulate cortex and other brain structures.

### RESULTS:

**Psychophysical Response:** In acupuncture, 82% of procedures induced *deqi* and 18% induced *deqi* mixed with sharp pain. In tactile stimulation, 37% evoked *deqi* and 63% did not evoke any specific sensation other than

Touch. Moreover, the intensity for *deqi* is much stronger in acupuncture than in tactile control.

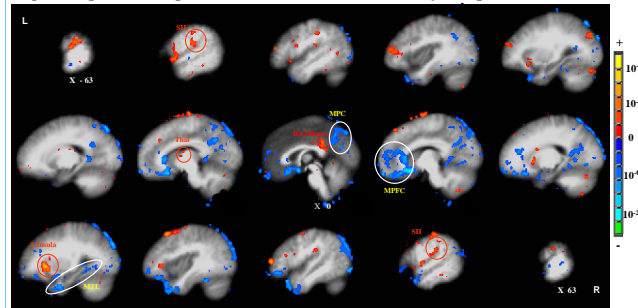
**Fig 2 Deqi Sensations: Acupuncture deqi vs Control**



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.

### Hemodynamic Response :

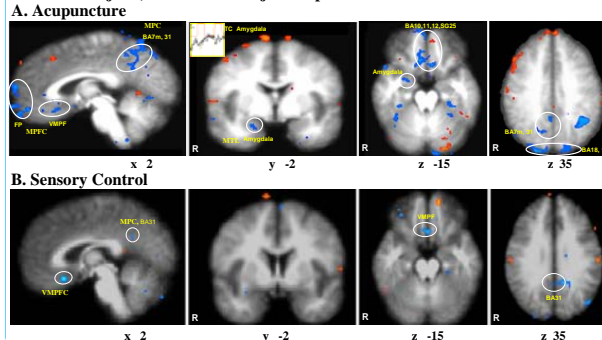
**Fig 3 Acupuncture deqi: 53 runs/37 subjects, p < 0.0001**



**Whole brain sagittal sections showing clusters of deactivated regions in the cortico-limbic network:** medial parietal cortex (MPC), medial prefrontal cortex (MPFC) and medial temporal lobe (MTL). **Activation** was more limited, occurring in the somatosensory cortex (SII), right anterior insula (A Insula), thalamus (Thal) and posterior cingulate (BA23 dor).

**Fig 4 A. B. Acupuncture Deqi vs Sensory Control**

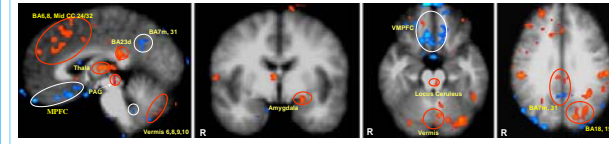
**Matched subjects, 26 runs/17 subjects p < 0.0001**



**A. Acupuncture:** Deactivated regions in the MPFC (BA10, 11, 12), pregenual and subgenual cingulate BA24/32, SG25, MPC (precuneus BA7m), posterior cingulate BA31), Medial temporal lobe (amygdala, parahippocampus).

**B. Sensory control:** The hemodynamic response was very limited compared with Acupuncture *Deqi* (See Fig 5). Focal signal deactivation was seen in VMPFC and MPC (BA31).

**Fig 5: Acupuncture Deqi + sharp pain 21 runs/15 subjects p < 0.0001**

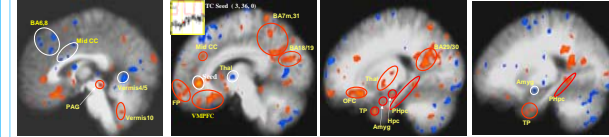


Compare with Acupuncture *deqi*, the deactivation of MPFC, MPC and MTL in *Deqi* (See Fig 3, 4A) was significantly attenuated. Activation became more prominent, appearing in the dorso-medial prefrontal cortex, the middle and posterior cingulate, the amygdala, PAG, vermis and the thalamus.

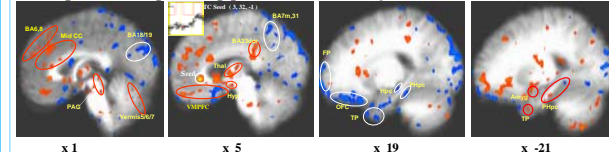
**Fig 6A.B. The functional connectivity (Seeding) in Cortico-limbic network (including pain matrix) deqi vs deqi+ sharp pain**

**Seed:** Pregenual cingulate cortex, Threshold  $p < 0.05$ .

**A. Acupuncture Deqi 23 runs/ 15 subjects (randomized)**



**B. Acupuncture Deqi + sharp pain 21 runs/ 15 subjects**



**A. Acupuncture deqi:**

**Positive correlation (circled in red):** Extensive coherent deactivation with: 1) MPFC(FP, VMPFC, ACC, MCC); 2) PMPC(PCN, RSC); 3) MTL(Amyg, Hpc, PHpc); 4) PAG; 5) TP; 6) OFC; 7) Vermis; 8) Thalamus; 9) BA18/19.

**Negative correlation (circled in white):** Limited coherent activation with: 1) MPFC (BA6,8, MCC); 2) Thalamus; 3) Vermis.

**B. Acupuncture deqi + sharp pain:**

**Positive correlation (circled in red):** Extensive coherent activation with: 1) MPFC(MCC, ACC); 2) MTL(Amyg, PHpc); 3) PAG; 4) Hypothalamus; 5) Vermis; 6) PMPC(PCC BA23dorsal); 7) Thalamus.

**Negative correlation (circled in white):** Coherent deactivation with: 1) PMPC(BA7,31); 2) OFC; 3) MTL(Hpc, PHpc); 4) TP; 5) 9) BA18/19.

**Table 1 ANOVA: Acupuncture deqi vs deqi+sharp pain ( subjects for Figures 5 and 6 )**

Structure	L/R	F-values		Anatomical		ANOVAs	
		X, Y, Z	F	%	F	%	F
mpfc_BA10_12	L	-436.6	4.98	442.0	4	3.89	4.28
mpfc_BA10_12	R	330.0	4.00	327.0	442	4.27	4.28
mpfc_BA31	L	-412.28	4.67	3.78	443	4.33	4.33
mpfc_BA31	R	3.7428	4.67	3.78	443	4.33	4.33
mtl_BA31	L	-403.4	4.59	4.02	443	4.33	4.33
mtl_BA31	R	372.62	4	3.78	443	4.33	4.33
amygdala	L	-322.45	3.69	3.62	447	4.37	4.37
amygdala	R	284.19	3.77	3.62	4	4.31	4.31
thp	R	222.45	3.67	3.62	4	4.28	4.28
thp	L	-151.98	3.28	3.49	4	4.28	4.28
ppc_BA7,31	R	-162.29	4	4.28	442	4.28	4.28
ppc_BA7,31	L	408.61	4	4.12	442	4.28	4.28
insula_m	L	-438.7	4.99	4.93	442	4.27	4.27
insula_m	R	322.64	4	4.12	442	4.28	4.28
pcc_BA12	R	348.2	4.02	4.03	4	4.29	4.27
pcc_BA12	L	-444.65	4.92	4.92	4	4.28	4.27
pvc_BA12	L	-448.29	4.92	4.92	4	4.28	4.27
pvc_BA12	R	444.65	4.92	4.92	4	4.28	4.27
slp_BA19	L	-383.52	4	3.83	442	4.33	4.33
slp_BA19	R	374.89	4	4.28	442	4.28	4.28
slp_BA19	L	-401.16	4	4.28	442	4.28	4.28
slp_BA19	R	404.22	4	4.28	442	4.28	4.28
hippocampus	L	-144.87	1.62	1.62	4	1.62	1.62
hippocampus	R	144.87	1.62	1.62	4	1.62	1.62
thalamus	L	-144.87	1.62	1.62	4	1.62	1.62
thalamus	R	144.87	1.62	1.62	4	1.62	1.62
vermis	L	-4.861	0.02	0.02	4	0.02	0.02
vermis	R	4.861	0.02	0.02	4	0.02	0.02
reticular	PAG	428.4	4	4.28	442	4.28	4.28
reticular	BP	428.4	4	4.28	442	4.28	4.28

$p < 0.001 / T > 3.36$ , minimal cluster = 3 voxels  
One way ANOVA  $p < 0.05 / T > 2.05$

**Abbrev. :**

PreCC, subCC, midCC, PCC : pregenual, subgenual, middle, posterior cingulate cortex.  
RF: reticular formation.

% : percentage signal change.

### ANOVA Results :

All the structures listed in the table showed significant difference by ANOVA. The results confirmed that acupuncture *deqi* elicited predominant deactivation in the limbic-paralimbic-neocortical system, including frontal pole, anterior, middle cingulate cortices, amygdala, hippocampus, Parahippocampus, Precuneus and cerebellar vermis.

**In contrast, acupuncture deqi + sharp pain activated most structures of the pain neuromatrix**, including anterior and middle cingulate cortices, amygdala, PAG, reticular formation, caudate, insula and cerebellar vermis.

### Discussion:

The hemodynamic response elicited by acupuncture is intimately correlated with the psychophysical response to acupuncture.

In accordance with previous reports on L14 and ST36 (3-4), acupuncture at LV3 with *deqi* showed marked deactivation in the limbic-paralimbic-neocortical network at multiple levels of the brain, including the cerebellum and brainstem. The deactivation was attenuated, or reversed in a large subset of the structures that belong to the pain neuromatrix in the concomitant presence of sharp pain. The response was coherent within the deactivation or activation network as evidenced by functional connectivity analysis. The activation pattern we observed has been reported in studies on pain, anxiety and psychostimulants (5-8). The limbic-paralimbic system plays a major role in the regulation and integration of emotion, cognition, autonomic and other brain functions, including the affective dimension of pain processing. The deactivation of the limbic-paralimbic-neocortical system may be the salient feature of acupuncture that accounts for its anti-pain, anti-anxiety, and other modulatory effects on multiple physiological functions.

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**Funding :** NIH, NCCAM: P01-AT002048-01,

R21-AT00978,  
F05 -AT003022-02

National Center for Research Resources  
MIND Institute