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The hybrid GLM–ICA investigation on the neural mechanism of acupoint ST36: An fMRI study

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ABSTRACT

Ample clinical reports and neuroimaging studies have demonstrated that the acupuncture has sustained effects after manipulation. However, most previous fMRI studies of acupuncture have paid little attention to this issue, only investigating on the manipulation effects. In the current study, we attempted to explore both acupuncture effects, which have positive influence to therapeutic efficiency, to reveal the neural mechanism of acupuncture. This paper combined the conventional general linear model (GLM) and independent component analysis (ICA) to study the topography and the temporal feature of brain activity to detect the brain responses to stimulation at ST36 (Zusanli) and a sham acupoint. The results showed that the manipulation-related effects and the sustained acupuncture effects separately induced statistically significant increases/decreases in the cortical-subcortical areas, including the anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (VLPFC), supplementary motor area (SMA) primary/secondary somatosensory cortex (SI/SII), occipital cortices and midbrain. Our findings suggested that the analgesia effects of ST36 integrated sophisticated physiological and psychological procedures. In addition, our results have shed light on methodology in acupuncture research.

Acupuncture, an efficient therapeutic modality in Traditional Chinese Medicine (TCM), has been accepted as an alternative and complementary therapy in western society [9]. Acupuncture has been used in treating a variety of symptoms in clinical practice. In the past decade, noninvasive functional magnetic resonance imaging (fMRI) techniques have provided us chances to investigate both anatomy and physiological functions related to acupuncture [5,10–14].

A large proportion of former experimental acupuncture researches have concentrated on the manipulation effect, which refers to the immediate brain response to needling [5,10–14]. However, certain clinical reports have indicated that the therapeutic effects of acupuncture can last several minutes/hours, or even days. Ng et al. concluded that the effective therapeutic effects lasted 10 weeks in the treatment of childhood persistent allergic rhinitis [20]. Price et al. demonstrated that the analgesic effects of acupuncture actually peaked long after acupuncture stimulation [25]. Further data analysis from our group stated that the sustained acupuncture effects altered the default mode network (DMN) and explored function-guide action of sustained acupuncture effects, combining spatial and temporal information [17,18]. Although evidence that the sustained acupuncture effects may exist is supported by these studies, the clinical practice also demonstrates that needling manipulation period and needling retention period, which refer to a single manipulation and a long resting period with needles in position, both contribute to its clinical effects. However, few studies have synthesized the analysis on acupuncture manipulation effects (AME) and the sustained acupuncture effects (SAE) to investigate the neural networks of acupuncture.

In this paper, we attempted to investigate the effects of acupuncture manipulation and the sustained acupuncture effects on a non-repeated event-related (NRER) paradigm [26], which consists a single BLOCK manipulation and long resting period, and it can be optimized to mimic the clinical condition as well as enables the focus on the both periods. Furthermore, we applied a hybrid hypothesis-driven and exploratory analysis for fMRI data by combining the conventional general linear model (GLM) and independent component analysis (ICA). ICA is a data-driven approach, which can separate the data mixed together into either spatially and temporally independent source. ICA does not only the remove high-frequency and low-frequency artifacts [19], but also it can isolates task-related neural networks [1,3]. The idea of hybrid GLM-ICA

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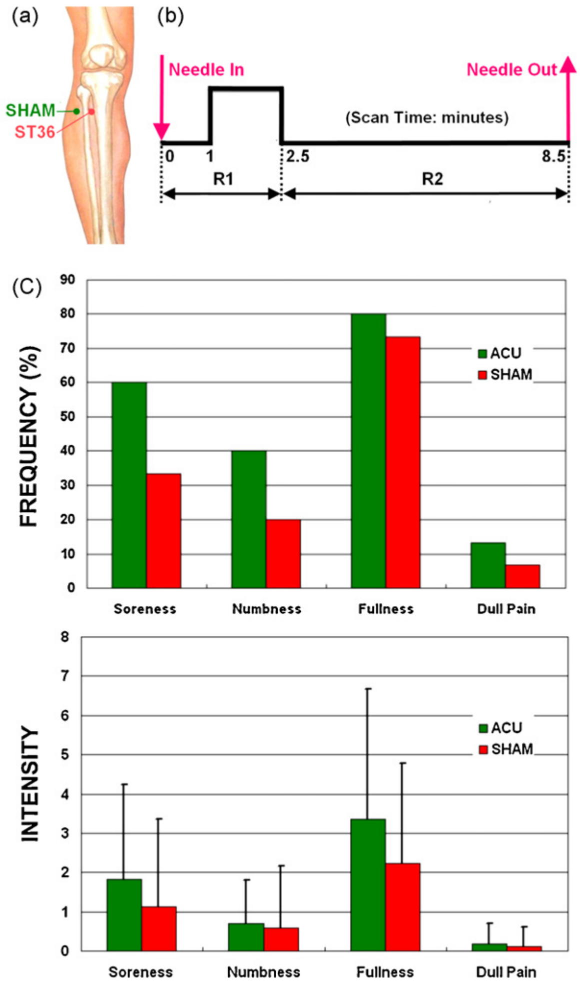

Fig. 1. (a) Experimental paradigm; (b) the epoch of acupuncture scanning lasted for 8.5 min. R1 was named as the manipulation state, and R2 was named as the post-stimulation state. (c) Results of psychophysical analysis.

was to produce the topography of brain activity during acupuncture manipulation using GLM and entered the GLM-related pattern of brain activity into ICA for exploring the brain spatial pattern associated with sustained acupuncture effects.

Eighteen healthy acupuncture naïve (9 male, 9 female and ages, 24.2 ± 2.9 years; mean ± SD)) right-handed Chinese subjects participated in this study. All the subjects had no history of neurological or psychiatric disorders and had refrained from alcohol or drug consumption in the previous 1 week. Every subject was given informed consent approved by the local review board for human studies.

The NRER paradigm was shown in Fig. 1b. A pure stainless steel disposable needle (0.2 mm in diameter and 40 mm in length) was inserted at acupoint ST36 on the right leg, located four finger breadths below the lower margin of the patella and one finger breadth laterally from the anterior crest of the tibia. And a non-meridian acupoint was chosen as the control, which located 2–3 cm apart from ST36 (Fig. 1a). Acupuncture treatment was performed by the same professional acupuncturist throughout the experiment. The depth of needle arranged from 2 cm to 3 cm and the needing was delivered in the balanced "tonifying and reducing" technique, rotating the needle clockwise and counterclockwise at 1 Hz for 1.5 min. Considering the aforementioned SAE, the subjects underwent sham acupuncture, and 2 days later, verum acupuncture. During scanning sessions, each subject was instructed to maintain head immobility with a foam pillow; the eyes were also covered with blinders and the ears were plugged with earplugs. All the subjects were asked to remain relaxed and focus on the acupuncture sensations. At the end of each scanning, the acupuncturist asked subjects whether they slept during the whole scanning or not. The subjects were then asked about the sensations they felt during scanning: aching, soreness, numbness, fullness, sharp or dull pain, pressure, heaviness, warmth, coolness, tingling, itching and any other sensations. The intensity of each sensation was measured using a 10-point visual analogue scale (0 = no sensation, 1–3 = mild, 4–6 = moderate, 7–8 = strong, 9 = severe and 10 = unbearable sensation), similarly to the studies from Hui et al. [10,11].

Functional MRI experiment was performed using a 3.0 T Signa (GE) MR with a standard head coil. Functional images were acquired with a single-shot gradient-recalled echo planar imaging (EPI) sequence (TR/TE: 1500 ms/30 ms, field of view (FOV): 240 mm × 240 mm, matrix size: 64 × 64, flip angle: 90°, in-plane resolution: 3.75 mm × 3.75 mm, slice thickness: 5 mm thick with no gaps, 32 sagittal slices). A set of T1-weighted high-resolution structural images was also collected (TR/TE: 2.7 s/3.39 ms, field of view (FOV): 256 mm × 256 mm, matrix size: 256 × 256, flip angle: 12°, in-plane resolution: 1 mm × 1 mm, slice thickness: 1 mm with no gaps).

Pre-processing was performed with SPM5 (SPM5, http://www.fil.ion.ucl.ac.uk/spm/). The first 4 time points were discarded to avoid the instability of the initial MRI signal. Images were realigned to the first image. If translation and rotation were more than 1 mm or 1°, the subject was excluded. The images were normalized to Montreal Neurological Institute (MNI) template and then smoothed using a Gaussian kernel with 6 mm full width at half maximum (FWHM).

To investigate AME, R1 data was extracted from the beginning point to 2.5 min. The pre-processed functional data for each subject was then submitted to a fixed-effects analysis, using the general linear model at each voxel. The design paradigm was convolved with a canonical hemodynamic response function, which was used as the reference function in the general linear model. Parameter estimates were assessed with least square regression analysis. The contrast of interest was the main effect of stimulation (verum or sham acupuncture) condition. Statistical parametric maps of the stimulation task minus baseline contrast were collected at each voxel. At the second-level analysis, the intra-group analysis was shown by adopting a one-sample t-test. A paired t-test was then applied to assessing differences between the verum and sham acupoints during the acupuncture manipulation. All of the contrasts were threshold at $p < 0.005$ (uncorrected) and the cluster size >3 voxels. In addition, the activating brain map of the intra-group analysis was used to create a mask by multiplying the binary values in each group, which was entered into assessing the brain response during the post-stimulation state using ICA. Here, we limited the voxels of interest with t-value > the threshold ($p < 0.005$, uncorrected).

To investigate SAE, R2 data extracted from 3 min to 8 min was arranged into Group ICA of the fMRI Toolbox (GIFT, http://icatb.sourceforge.net/). For each individual, the scans were analyzed with spatial independent component analysis to decompose the data into 20 components using the Informax ICA algorithm [2], which is based on Akaike's information criterion (AIC). The acupuncture post-stimulation-related component was identified by spatially correlating the entire components with the mask created during the acupuncture manipulation mentioned above. For each subject, the best-fit component from each session of the task (verum or sham acupuncture) was then separately converted to z values, which was selected as the post-stimulation-related component. At the second-level analysis, the steps were similar to the ones in GLM processing.

The prevalence of these sensations was expressed as the percentage of individuals in the group that reported the given sensations (Fig. 2a). And the intensity of sensations was expressed as

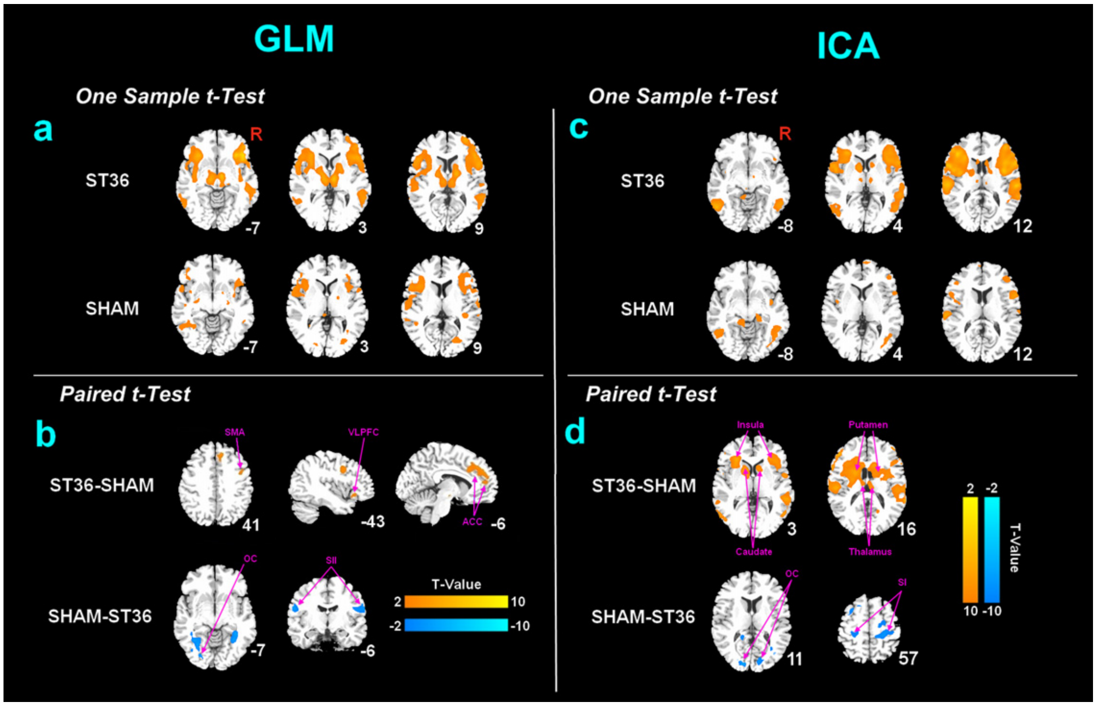

Fig. 2. Brain regions showing significant increases/decreases during manipulating, using GLM or ICA. The 2nd level analyses was threshold at $p < 0.005$ (uncorrected) and the cluster size >3.

the mean score ± SD (Fig. 2b). Soreness, numbness and fullness were primary Deqi sensations in the current study. Mean soreness was 1.82 (S.D. = 2.40) and 1.12 (S.D. = 2.23), mean numbness was 0.71 (S.D. = 1.10) and 0.59 (S.D. = 1.58), mean fullness was 3.35 (S.D. = 3.32) and 2.24 (S.D. = 2.56) for ST36 and sham, respectively. There was not significant differences in intensity among the three acupoints, based on 95% confidence interval (soreness: $p = 0.38$; fullness: $p = 0.80$; numbness: $p = 0.29$; dull pain: $p = 0.10$).

The results of AME using GLM analysis were shown in Fig. 2b and Table 1 (GLM). And the stimulation of ST36 manipulation induced statistically significant increases in several cortical areas, including the rostral anterior cingulate cortex (rACC), doral anterior cingulate cortex (dACC), ventrolateral prefrontal cortex (VLPFC), supplementary motor area (SMA) and midbrain, and decreases in the primary somatosensory cortex (SI), secondary somatosensory cortex (SII), and certain occipital cortices.

During the SAE period, the 4th component of the ST36 data and the 16th component of sham were the best-fit ones (spatial correlation: ST36 = 0.52 and sham = 0.41). And ST36 induced significant increases in the insula, caudate, putamen, thalamus and midbrain. Additionally, decreases were detected in the SI, SII, and occipital cortices (BA 17/18/19) (Fig. 2d and Table 1 (ICA)).

In this study, we focused on both AME and SAE and employed a hybrid GLM-ICA approach to investigate the responses of central neural system (CNS) to acupuncture stimulation at an analgesic acupoint (ST36) and a sham point. The results demonstrated that acupuncture manipulation at ST36 mainly induced increases in the ACC, VLPFC and SMA, and decreases in the SI and SII. The brain regions were related with pain sensory, pain affective and opioid systems. In addition, the influence derived from the acupuncture manipulation were extended to the resting period after needing, and induced activations in a large extension of brain regions, including the insula, caudate, putamen and thalamus. The findings were likely to disclose the neural modulatory mechanism underlying acupuncture analgesia acupoint.

Neuroimaging studies have implicated that VLPFC drives top-down pain inhibitory network in pain perception, anticipation and experience of pain. Lieberman et al. found that activation of the right VLPFC was associated with pain relief in irritable bowel syndrome [16], and Salomons et al. detected the VLPFC's critical role in predicting the pain rating difference [28]. It is reported that ST36 is one of the important acupoint for analgesia treatment in abundant clinical trials [15,32]. We proposed that the analgesia mechanism underlying ST36 was possibly accounted for increases in the VLPFC, which inhibited certain pain perception.

It is generally accepted that mediation on endogenous opioid is a key component of acupuncture analgesia. Moreover, collective results from pain and placebo studies show that rACC is a crucial cortical area implicated in opioid analgesia in pain and/or placebo studies. Petrovic et al. demonstrated that the rACC and the brainstem were activated during both opioid and placebo analgesia using positron emission tomography (PET) [23]. Moreover, rACC is related with cognitive modulation of pain processing [22] and contextual modulation of experience of pain [24]. On the other hand, dACC is known to subserve cognition, motor control and reward assessment/decision. Furthermore, dACC was detected as a critical region involved in the unpleasantness felling of physical pain [16,27]. Therefore, we further suggested that acupuncture analgesia induced by ST36 might be involved in both high cognitive networks and opioid systems.

With comparison to sham, decreases in the SI and SII were significantly observed via verum group. Pain starts when sensory signals from the spinal cord get to the brain via the thalamus and are sent to SI and SII [33]. Furthermore, SI and SII are implicated in the sensory-discriminative aspects of pain processing (such as intensity determination, location of nociceptive stimulation [31]), as components of the sensory pain networks [33]. We speculated that decreases in the SI and SII might be due to that ST36 inhibited or modulated pain sensory for analgesia effects.

Of interest, the extensive increases in the insula and subcortical areas were detected during the SAE period. Insula is wide connected with cortex, subcortex and brainstem structures [4]. And the function of insula is involved in decisions and subsequent behavior,

Table 1
Main localizations deriving from GLM or ICA by comparing ST36 vs. sham using a paired *t*-test.

Regions	Hem	ACU-sham (GLM)					ACU-sham (ICA)				
		BA	Talairach			*t*-Value	BA	Talairach			*t*-Value
			x	*y*	*z*			*x*	*y*	*z*	
dACC	L										
	R	24/32	12	22	24	3.24					
rACC	L										
	R	32	12	44	9	3.14					
VLPFC	L										
	R	47	42	26	−9	3.04					
SMA	L										
	R	6	45	2	33	2.85					
Midbrain	L										
	R		9	−9	−12	2.80		9	−12	−2	2.81
SI	L	3/2	−42	−21	40	−3.43	3/2	−24	−29	62	−5.64
	R	3/2	48	−15	48	−3.91	3/2	24	−29	65	−6.57
SII	L	40/43	−59	−8	20	−3.32	40	−39	−27	46	−2.78
	R	40/43	62	−5	17	−3.43	40/43	39	−27	46	−4.04
Occipital cortex	L	17/18/19	−18	−84	7	−2.89	17/18/19	−15	−83	21	−2.81
	R	17/18/19	21	−75	12	−2.87	17/18/19	15	−84	7	−3.11
Insula	L						13	−33	21	7	4.52
	R						13	39	9	8	4.19
Caudate	L							−12	12	2	5.05
	R							12	18	13	4.84
Putamen	L							−15	9	2	5.66
	R							24	−8	9	3.98
Thalamus	L							−6	−17	17	3.99
	R							9	−17	17	4.66

Abbreviations: BA—brodmann area; Hem—hemisphere; rACC—rostral anterior cingulate cortex; dACC—doral anterior cingulate cortex; VLPFC—ventrolateral prefrontal cortex; SMA—supplementary motor area; SI—the primary somatosensory cortex; SII—the secondary somatosensory cortex; L—left; R—right.

emotional experience and pain-related modulation. Recently, fMRI imaging data provided that the anterior insula played an important role in the cognitive control of task switching, particularly in a dynamic switching between the central-executive network and the DMN [29]. Given acupuncture may mediate the neurophysiological system with brain regions related to self-control and self-regulate to restore homoeostasis, we suggested that insula could be likely related to monitoring the sustained modulation of acupuncture effect, as an crucial hub in the internally sensed changes. Activation of the putamen is related with painful stimulation [8]. Chudler and Dong found that some neurons in the basal ganglia were believed to process and integrate somatosensory information [7]. Pastor et al. indicated that putamen was an important role in the perception of temporal features of tactile and auditory stimuli [21]. Furthermore, the caudate–putamen is recruited in pain and nociception [6]. Caudate is implicated in dopamine release [30]. The thalamus is believed to both process and relay sensory information selectively to various parts of the cerebral cortex. In pain studies, thalamus is also a party of sensory pain networks [33]. In the current study, it was possible that subcortical activity might be recruited in relay of nociceptive transmission or modulation of pain sensory, which possibly attributed to the sustained analgesia effects of ST36.

In summary, by applying a hybrid GLM–ICA analysis method, this study accessed AME and SAE at ST36 and a sham point, inducing increases/decreases in the VLPFC, ACC, SI, SII, insula, caudate, putamen, thalamus and certain midbrain were implicated in instant effects and sustained effect of analgesia at ST36. The current results suggested that the analgesia effects of ST36 might be involved in complexly physiologic and psychological processing. Additionally, the mechanism underlying acupuncture was not well-defined to date. It is essential to use proper approaches to acupuncture studies. Therefore, our findings reflected a significant methodological contribution combining with GLM and ICA.

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