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Activation of the hypothalamus characterizes the response to acupuncture stimulation in heroin addicts

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Abstract

Acupuncture stimulation elicited a composite of sensations termed *deqi* that is related to clinical efficacy. Neurobiological studies have identified the hypothalamus as an important component in mediating the *deqi*. Functional changes in hypothalamus persist after abstinence in addicts. We investigated the activation in the hypothalamus associated with acupuncture stimulation in healthy volunteers and heroin addicts by fMRI. Cortisol level and psychophysical responses, including the *deqi* sensation (an acupuncture effect of needle-manipulation), anxiety, and sharp pain, were also assessed. The activation of the hypothalamus was more robust in the addicts than that in the healthy subjects during acupuncture stimulation. The *deqi* scores of the heroin addicts were significantly higher than those of the healthy subjects during acupuncture treatment. An acupuncture sensation scale predicted the activation of the hypothalamus associated with the *deqi* sensation.

Keywords: Acupuncture; Hypothalamus; Cortisol; Heroin addicts

Acupuncture stimulation typically elicits a composite of sensations termed *deqi* (the effect of the characteristic needle-manipulation sensation, which manifests as numbness, heaviness, distention, and soreness), which is believed to be a trait characteristic in achieving a therapeutic effect, according to traditional Chinese medicine. A body of scientific evidence indicates the importance of the *deqi* sensation for acupuncture treatment outcomes [8,6]. Neurobiological studies on acupuncture at commonly used acupuncture points have identified the hypothalamus and limbic system as the important components in mediating the acupuncture effects and *deqi* [9,3,21,19,14].

Almost of these earlier studies assumed that all subjects were responding similarly to acupuncture stimulation and acquired the similar *deqi* sensation. In fact, the *deqi* sensation depends on the psychophysical response to needle-manipulation. In clinical practice, even healthy subjects can differ dramatically from one another in their sensitivity to acupuncture and *deqi. Deqi* may be an important variable in studies of the efficacy and mechanism of the action of acupuncture treatment.

Recently, acupuncture or electroacupuncture (EA) has been applied, with great success, to attenuate various conditions related to drug addiction [15,2]. It has been generally accepted that the addicted brain is distinctly different from the non-addicted brain, as manifested by changes in brain metabolic activity, receptor availability, and gene expression [12,10]. The confirmed neuroendocrine finding among opiate or cocaine users is hyperactivity of the hypothalamic–pituitary–adrenal (HPA) system [11,1]. Plasma cortisol and ACTH are elevated in heroin addicts on the day of admission into treatment centers, and heroin-dependent individuals often display abnormal patterns of hypothalamus hyperactivity [13].

In the present study, we investigate the effects of acupuncture stimulation to normal individuals and addicts differing widely in their levels of the *deqi* sensation with the purpose of testing

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two ideas. (1) Is the hypothalamus differentially activated by the degree to which a given individual is sensitive to acupuncture as measured by a psychophysical rating of needling sensation (*deqi* score)? Such findings can help address the efficacy and mechanism of the action of acupuncture treatment. (2) Given that opiate or cocaine addict is hyperactivity of the hypothalamic, does addict respond differently to acupuncture, and the response to acupuncture stimulation in addict characterize strong activation of the hypothalamus, compared with healthy subject?

We administered a psychophysical rating of needling sensation (*deqi* score) to determine the different responses to acupuncture in heroin addicts and healthy subjects during acupuncture stimulation. We performed functional magnetic resonance imaging (fMRI) on heroin addicts and healthy subjects to detect differences in the levels of activation in the hypothalamus. We also measured plasma cortisol, a stress hormone produced in the hypothalamus, in heroin addicts and healthy subjects.

Six right-handed healthy men (mean age 29.1 ± 6.1 [S.D.] years) and six right-handed male heroin addicts (mean age 30.2 ± 7.5 [S.D.] years), all of whom were naive to acupuncture, participated in the study. All healthy subjects were screened and excluded for neurological, mental and medical disorders. The heroin addicts had a mean history of 41.5 (S.D. = 9.8) months of heroin use and their mean dosage per day was 1.2 g (S.D. = 0.4). The participants were allocated to test brain activation due to acupuncture using fMRI, and were asked to quantify the intensity of the *deqi* sensation, sharp pain, and anxiety at the end of the scan. Experiments were conducted with the understanding and written consent of each subject and approval of the human subjects committee at the Ningbo Addiction Research and Treatment Center in Ningbo, China. All the subjects were free to withdraw from the experiment at any time. The subjects were screened for other neurological, mental, and medical disorders and were excluded if any such disorders were found. On the day of testing, all 6 heroin-addicted patients took heroin (the duration between the last heroin intake and scanning ranged from 3 to 7 h). At the time of scanning, no patient exhibited any symptoms of heroin withdrawal.

On the day of testing, anatomical scans of the brain were collected prior to acupuncture imaging. All the subjects were instructed to lie still and keep their eyes closed during the scan. They underwent manual acupuncture at acupoint ST36 (located 5 cm below the lateral flank of the knee joint) on the left leg. Acupoint ST36 was chosen because it is the most frequently used acupoint in the treatment of drug addiction [2,18]. A disposable sterile stainless steel acupuncture needle, with a diameter of 0.25 mm and a length of 30 mm, was inserted into ST36 by the acupuncturist. The rotation frequency was approximately 180 rotations per minute at an angle of 45° from the perpendicular to the skin surface. The *deqi* sensation that develops at the site of acupuncture stimulation was induced carefully. This approximates a technique used in clinical practice. The total scanning time was 11 min per run. The needle was kept in place for 2 min prior to needle-manipulation. The block design for acupuncture was R–A–R–A–R–A–R–A–R–A–R, with “R” representing rest and “A” representing stimulation (see Fig. 1).

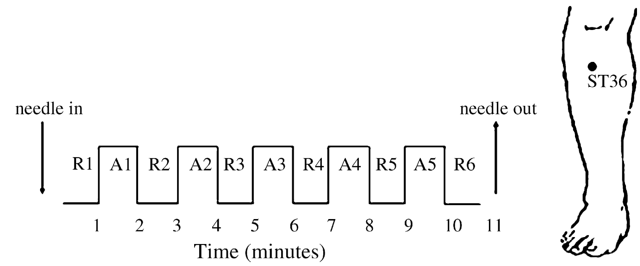

Fig. 1. Acupuncture was performed at acupuncture point ST 36 (solid circle). The acupuncture needle was inserted and adjusted to tolerance prior to each scanning run. After remaining at rest for 2 min, the needle was rotated bidirectionally. The needle was removed at the end of the 11-min experimental run. The signal intensities without needle-manipulation served as the baseline for comparison with the signal intensities during manipulation.

At the end of the 11-min scan, the subjects used a 10-point scale to self-rate the perceived intensities of the *deqi* sensation, sharp pain, and anxiety [19,6]. A score of 0 indicated no intensity at all, a score of 1–3 indicated mild sensation, a score of 4–6 indicated moderate sensation, a score of 7–8 indicated strong sensation, a score of 9 indicated severe sensation, and a score of 10 indicated unbearable intensity. In order to minimize bias, subjects participated in a psychophysical training session in which they rated different needle-manipulation prior to the test procedures. These data are not reported further. The *deqi* score was simplified as an overall combination of several sensory perceptions, including pressure, soreness, fullness, distension, numbness, tingling, local warm sensations, dull pain, and the spreading of these sensations.

All functional MR scanning was performed using a 1.5 T Siemens Sonata scanner. Fast Spin Echo high-resolution T1 images in the transverse direction (TR = 500 ms, TE = 7.7 ms, Matrix = 256 × 256, FOV = 220 mm × 220 mm, 25 slices, 4 mm thickness with 1 mm inter-slice gap) were obtained for structural information covering the whole brain. Functional images were acquired by the Echo Planer Imaging sequence in the identical position to the T1 images (TR = 3000 ms, TE = 60 ms, Matrix = 64 × 64, FOV = 220 mm × 220 mm, 25 slices, 4 mm thickness with 1 mm inter-slice gap).

Functional data were processed with AFNI (Analysis of Functional NeuroImages) software. The first three volumes, which corresponded to the stabilization period of the magnetic signal, were not considered for further analysis. The dataset for each run was temporally smoothed and realigned to compensate for small movements. Statistical parametric mapping was completed via a generalized linear model. The estimated response function was then compared, using a *t*-test, to the time series data for each brain voxel (3dDeconvolve, AFNI). The statistics were color-coded and mapped onto the subject’s own high-resolution 3D anatomical data set in Talairach space. For each individual analysis, data from duplicate runs of acupuncture at acupoint ST36 were averaged. The data were then transformed into Talairach space, and normalized to the average image intensity. The level of significance was thresholded at $P < 0.01$ ($t > 2.63$) and a minimum cluster size of 2 voxels. The time course of a signal change was visually compared with the experimental paradigm. Signal changes that failed to agree

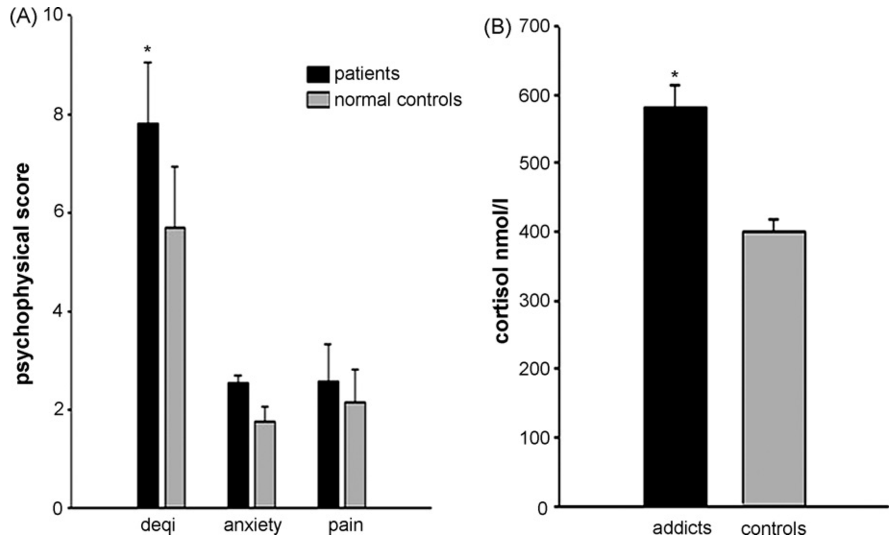

Fig. 2. The bar graph shows the average psychophysical responses (A) and Cortisol responses (B) after acupuncture stimulation. Data are expressed as mean values ± S.E.M. Statistically different from the control group ($^{*}P < 0.001$).

with the paradigm were rejected as artifacts. In group analysis, group-averaged functional statistical maps were registered onto the group-averaged high-resolution anatomical maps of the subjects.

To search for activated areas that were consistent for the whole group of subjects, a voxel-wise fixed-effect group analysis was performed as well. In this case, the time series from each subject was z normalized and concatenated prior to the statistical computation. The resulting group activation maps were thresholded with the same procedure used for the individual maps and superimposed on the Talairach transformed structural scan of one of the subjects. To test the hypothesis that heroin addicts would show more BOLD signal changes in response to acupuncture compared to matched controls, we performed an independent samples t-test between the groups ($a = 0.05$, two-tailed). This t-test compared the coefficients representing the relationship between the observed signal across the time series and the reference vector coding the hypothesized signal fluctuations over the experiment.

To better understand the *deqi* sensation and cortisol levels of both the heroin-addicted patients and the normal controls to acupuncture stimulation, we administered acupuncture stimulation to a larger sample of 45 Chinese men, consisting of 25 heroin addicts (mean age = 31.2 years), who were drawn from the same clinical population as the patients who were scanned, and 20 normal controls (mean age = 27.8 years). These two groups were matched in terms of age and general intellectual ability. The paradigm of acupuncture manipulation is the same method for the fMRI scanning test.

All subjects received acupuncture stimulation at 8:10 to 10:00 A.M. Stimulation was conducted for 15 min. Blood samples were drawn immediately after acupuncture stimulation. Blood samples were immediately centrifuged in the cold and the plasma was frozen at −80 °C until assayed. Cortisol plasma concentrations were measured utilizing a competitive enzyme immunoassay by a kit from ICN Biochemicals (Costa Mesa, CA). After acupuncture stimulation, the subjects used a 10-point scale to self-rate the perceived intensities of the *deqi* sensation, sharp pain, and anxiety.

One-way or two-way analyses of variance (ANOVA) were used in the analysis of the differences among the three psychophysical scores and plasma cortisol levels. Pearson analysis was used for the correlations between the activated voxel rate in the hypothalamus and *deqi* score.

As shown in Fig. 2A, the *deqi* scores of the heroin addicts were significantly higher than those of the healthy subjects during acupuncture treatment ($F_{1,44} = 33.18$, $P < 0.001$). Fourteen of the 45 subjects reported anxiety ratings of 0 during acupuncture stimulation. The average anxiety ratings were 2.55 for the heroin addicts and 1.76 for the healthy subjects. There were no significant differences between the patient group and control group. Compared with the *deqi* sensation, acupuncture caused significantly less sharp pain. There were no significant differences in sharp pain sensation between the healthy subjects and the heroin addicts ($F_{1,44} = 3.53$, $P = 0.067$).

Cortisol secretion differed between the two groups of subjects after acupuncture stimulation (Fig. 2B). Compared with the control group, heroin addicts receiving acupuncture stimulation exhibited higher cortisol response (heroin addicts: 581.41 ± 31.43 versus normal controls: 401.43 ± 15.60; $P < 0.01$).

As shown in Table 1, ROI analysis provided correlation coefficients for the heroin addicts and the healthy subjects, which were to be compared. Activation in the right hypothalamus was stronger—that is, the correlation coefficients were higher—in the heroin addicts than in the healthy subjects ($P < 0.025$). The heroin addicts exhibited significantly less activation than the healthy subjects in the right thalamus and parahippocampal ($P < 0.025$).

To examine whether individual *deqi* sensation was associated with the hypothalamus activation, the correlations between individual *deqi* score differences and regional activities were

Table 1
Significant brain activation of the control subjects and heroin addicts during acupuncture stimulation

Region	Side	Talairach[a]			Effect size (*d*)[b]
		X	*Y*	*Z*	
Heroin addicts > controls[c]:					
Hypothalamus	R	2	−3	−8	2.15
Controls > heroin addicts[c]:					
Thalamus	R	−2	−16	12	1.96
Parahippocampus	R	18	−4	−28	2.03

[a] Coordinates refer to voxel of maximum intensity within cluster.
[b] Cohen's *d* = standardized mean difference for effect size of group difference.
[c] $P < .025$.

analyzed using the same ROIs as described above. The regional brain activity was calculated using the activated voxel rate within the ROIs. As shown in Fig. 3, the right hypothalamus activation was significantly associated with the *deqi* score: the right hypothalamus activation showed statistical significance in the Pearson correlation ($r = 0.67$, $P < 0.05$).

Functional neuroimaging studies suggested that the hypothalamus was activated during acupuncture stimulation [3,21], but recent work has obtained contradictory results [6]. This might be explained by some variable factors, such as legitimacy of acupuncture points, variable needling methods, intensity of acupuncture stimulation, and study subjects who can be good or poor responders. Scientific evidence of the importance of the *deqi* sensation in studies of the efficacy and mechanism of the action of acupuncture treatment is limited. One trial showed that *deqi* was the predictor of a positive outcome in osteoarthritis [17]. More recently, another study compared the analgesic effects of three acupuncture modes in a cohort of healthy subjects. They suggest that attributes of the *deqi* sensation may be useful clinical indicators of effective treatment [8]. We extended this analysis to the neurobiological level by exploring whether individual differences in the *deqi* sensation modulate the degree to which the hypothalamus is activated by acupuncture stimulation. We found that the hypothalamus activation was significantly associated with the *deqi* score. These results suggest that individual differences in the *deqi* sensation should be considered carefully in acupuncture research.

In present study, an important finding was that the activation in the hypothalamus during acupuncture stimulation was more robust in the heroin addicts than in the healthy subjects. Cortisol levels were significantly higher in the heroin addicts than in the healthy subjects after acupuncture stimulation. It has been generally accepted that the hypothalamic–pituitary axis provides a multidimensional integration of neuroendocrinal and autonomic homeostasis. The hypothalamus, which has the most abundant endorphinergic neurons and long descending projec-

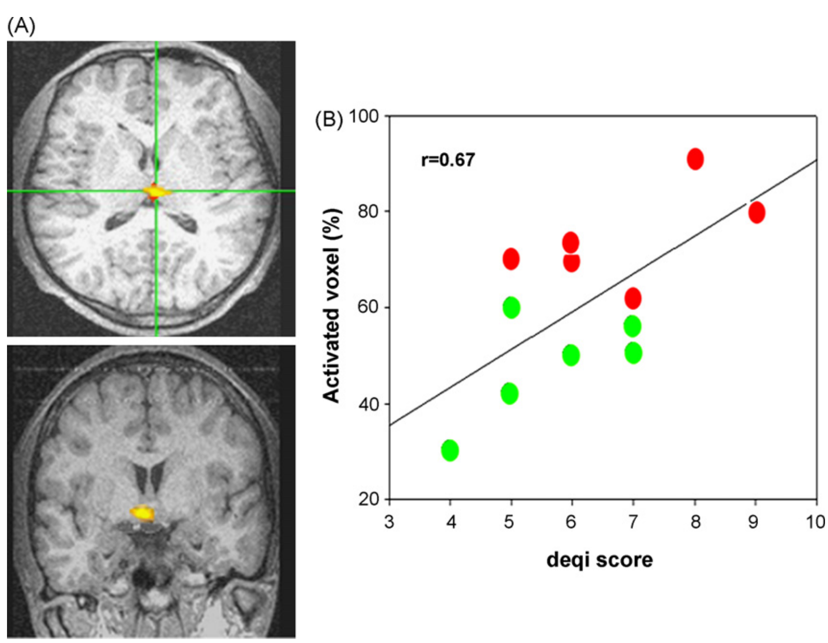

Fig. 3. Individual differences in the *deqi* scores are a critical variable for the detection of the hypothalamus activation during acupuncture stimulation. (A) AFNI whole-brain, voxel-wise *t*-map image of group differences depicting greater activation of the right hypothalamus in heroin addicts (vs. healthy controls) during acupuncture stimulation. (B) Regression plots showing correlation ($r = 0.67$, $P < 0.05$) of *deqi* scores with the activated voxel rate in the hypothalamus (red circle, the heroin addicts; green circle, the healthy subjects).

tions to the raphe nucleus and periaqueductal gray matter of the mesencephalon, has repeatedly been shown to be critical in acupuncture analgesia [7,19]. Long-term heroin use causes functional changes in the hypothalamus that persist long after abstinence. Both prolonged opiate and cocaine abuse induce an increased hypothalamic–pituitary axis activation to a pharmacological stressor [1]. The present study is consistent with the previous reports that the activation of hypothalamus is sensitive to acupuncture stimulation in heroin addicts. Another finding in present study was that the heroin addicts showed less activation than healthy subjects in the thalamus and parahippocampus. This may be explained by differences in activity of the thalamus and parahippocampus in heroin addicts and healthy subjects. A number of studies have shown that acupuncture needle-manipulation modulates the limbic system [5]. The repeated use of heroin could induce abnormal activity in thalamus and parahippocampus [10,11].

A body of clinical and experimental evidence indicates that the presence of the *deqi* sensation is a prerequisite for, and often an indicator of, a clinical acupuncture effect. Traditionally, patients are asked to remain aware of the sensation during acupuncture treatment. *Deqi* may be an important variable in studies of the efficacy and mechanism of the action of acupuncture treatment. The present study showed that the *deqi* sensations of heroin addicts were significantly higher than those of healthy subjects during acupuncture stimulation, indicating that heroin addicts are "good" responders to acupuncture stimulation. The present findings may also help clarify the clinical observation that acupuncture analgesia is different in heroin addicts than in healthy subjects. It is notable that the present study represents a short-term effect of acupuncture stimulation in heroin addicts (only one 11-min session of acupuncture stimulation). The effects of repeated and long-term acupuncture stimulation on the activation of an addict's dysfunctional hypothalamus remain unclear.

Recent functional brain mapping studies conducted on healthy subjects have demonstrated that acupuncture stimulation at analgesic points, such as L14 and ST36, may modulate the hypothalamus–limbic system [19,4,20]. Wu et al. found that the hypothalamus had a tendency for sustained activation on the MR images obtained after acupuncture [19,6]. In agreement with the clinical observation that acupuncture at the L14 acupoint has a stronger analgesic effect than at the ST36 acupoint, previous studies suggest that acupuncture at L14 activates the hypothalamus more extensively than does acupuncture at ST36 [19]. Our finding that the hypothalamus activation was significantly associated with the *deqi* score evoked by acupuncture treatment further supports evidence that the hypothalamus might characterize the central expression of acupuncture stimulation and serve as one of the key neural substrates in mediating the efficacy of acupuncture stimulation. Because attributes of the *deqi* sensation may be useful clinical indicators of effective treatment clinically, the acupuncture treatment outcomes in different patients may be predicted by the functional activation of the hypothalamus.

With regard to the study protocol, there are some variable factors that need to be taken into account. Firstly, we cannot completely exclude the possibility that the intense stressor itself can interfere with acupuncture stimulation and activate several brain regions. However, in present study, we did not observe any signs of stress in the healthy subjects and the heroin addicts (such as heart rate, blood pressure, unpleasantness, or anxiety) during acupuncture stimulation. In fact, Smith and coworkers found that patients who had completed acupuncture stimulation often continued to enjoy stress reduction induced by occasional "booster" acupuncture treatments [16]. Secondly, as these observations were made in a relatively small cohort of subjects, further testing in clinical populations is warranted. However, acupuncture-imaging studies of a similar or smaller size have yielded interesting and innovative findings and provided impetus to further investigations. These preliminary results may be of importance for the design of further confirmative studies.

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