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Neural activities in human somatosensory cortical areas evoked by acupuncture stimulation☆

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KEYWORDS
Cortical inflation;
Tactile;
Functional MRI;
fMRI;
Brain mapping

Summary
Objectives: To investigate neural representation evoked by acupuncture from human somatosensory cortices, especially from primary (*SI*) and secondary (*SII*) somatosensory areas.
Design and setting: Neuroimaging study — Blood-oxygenation-level-dependent (BOLD) functional MRI was performed during acupuncture on *LI4* ($n = 12$ healthy participants). Sham acupuncture and innocuous tactile stimulation were also applied on the same acupuncture site as control comparisons.
Outcome measures: Responsive neural substrates were visualized and identified based on both individual and group-level surface activation maps.
Results: Discrete regions within the precentral gyrus (area 4) and the fundus of the central sulcus (area 3a) were selectively activated during the real acupuncture stimulation. In *SII*, the activation was extended in a postero-inferior direction to the fundus of the lateral sulcus.
Conclusion: This specific pattern of acupuncture-related activation indicates that deep tissue stimulation (as seen in area 3a activation) and concurrent processing of sensory stimulation (as seen in activation in *SII*) may mediate neural responses to manual acupuncture.

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Introduction

Acupuncture has become an important alternative treatment modality for chronic and acute pain.[1,2] However, mechanisms of action underlying acupuncture analgesia are still not understood well.[3] Research has focused on numerous candidate mechanisms thought to operate peripherally, spinally and/or at the supraspinal level.[4–7] Well-studied mechanisms include acupuncture's role as a peripheral effector of endogenous opioid peptide release,[3] where pain relief has been reversed through naloxone administration.[8] Studies also suggest acupuncture may act as a modulator of the dorsal horn neurons that gate pain at the level of the spinal cord, or may exert specific central effects on limbic and paralimbic structures.[5,7,9]

Although there is little consensus on the different ways that peripheral, spinal and supraspinal mechanisms may work together to elicit an acupuncture effect, a concurrent line of research suggests that the somatosensory character of the needling sensation, — called '*deqi*' (often described as a 'dull achy sensation') — is related to acupuncture's therapeutic effectiveness.[10,11] If the needling sensation is a specific component of the signal delivered by the acupuncture needle, we would expect cortical structures involved in the processing of somatosensory sensation to be specifically modulated by acupuncture.

Recent advances in neuroimaging research allow us to begin to assess the somatosensory signal hypothesis by evaluating acupuncture's effects on multiple somatosensory cortical areas, each associated with different types of perceptual function. These somatosensory cortical areas are somatotopically organized and include the classical somatosensory cortex area 3b (Brodmann's area—-BA, studied by Penfield[12]) located in the rostral portion of the post-central gyrus. In humans and in primates, studies have shown that area 3b responds to light touch stimulation and is bordered on the anterior side by area 3a, located in the fundus of the central sulcus.[13] Immediately caudal to 3b is area 1, associated with both tactile stimulation and pain, and area 2, associated with orienting the direction of tactile stimulation.[13,14]

Because the '*deqi*' sensation is typically described as a ''deep'', ''achy'' sensation, we hypothesized that real acupuncture would specifically elicit more activation in area 3a, the area associated with deep, proprioceptive stimulation, when compared with a non-penetrating sham needle using the same insertive procedure for both stimuli. For the purpose of shedding further light on map area boundaries distinguishing area 3a from area 3b, we used a paradigm developed by Moore et al.,[13] in which light tactile stimulation is applied to visualize a boundary between area 3b (light touch/tactile) and area 3a (deep tissue stimulation). In order to localize the activations that are obscured by the curvature in sulcal and adjacent gyral structures, we adopted 3-dimensional cortical inflation techniques, which unfold the gyri (thus revealing deep gyral structure).

Methods

Subjects

The study was approved and conducted in accordance with the local Institutional Review Board of Brigham and Women's Hospital. A total of 12 individuals (three females, ages ranging from 20 to 39 years old, mean age = 25.2 ± 6.5) without a history of neurological or psychiatric conditions participated. Participants at the time of scanning were free of any transient medical problems or symptoms. The majority of participants were naïve to acupuncture stimulation ($n = 9$) and were right-handed ($n = 11$) according to the Edinburgh Handedness Inventory. Three participants had previous experience with acupuncture. All participants were blinded to the sequence and type of stimulation throughout the experiment.

Pre-fMRI testing

Prior to the fMRI exam, both acupuncture and sham acupuncture stimulation were applied to *Large Intestine 4* acupoint (*LI4*; located in the dorsum of the hand, the first interosseus space) in order to lessen any psychological uneasiness toward needle stimulation. The characteristic feeling of *deqi* phenomena (often characterized as numbness, distention, heaviness, fullness, or soreness[10]) was verbally described to participants who were then asked to rate the extent to which each stimulus resembled the described sensation (while remaining blind to the identity of the real and sham acupuncture stimuli). Our intention in conducting this preliminary procedure was (1) to reduce possible confounding effects of any emotional or cognitive response toward first-time exposure to acupuncture (2) train participants to rate their responses to stimuli.[15] First, a small plastic ring was applied to the designated insertion point to hold the needles in place. Stimulation was applied to *LI4* on the right hand for approximately 10 s. A disposable, sterile MR-compatible silver #36-gauge acupuncture needle was inserted to a depth of less than 1 cm (~0.3 cun). Stimulation was delivered by gentle manual rotation of about 2 Hz. Using the same initial ritual (including twisting action at a same rate and force to mimic the process of real acupuncture), sham acupuncture was also delivered using a non-penetrating sham needle[16,17] to the same location. This blunt needle with a retractable shaft is experienced as similar to the typical, therapeutically-designed acupuncture needle. Each participant was able to describe the sensation associated with typical *deqi*. All participants completed the pre-fMRI session without emotional distress related to the acupuncture.

Imaging stimulation paradigm

Each participant was positioned supine with the hand and wrist areas exposed outside of the magnet bore opening; the acupuncturist was readily able to access stimulation location. Participants' head motion was limited using MR-compatible cushions. The study consisted of three separate fMRI sessions and stimulation conditions: (1) real acupuncture stimulation, (2) sham acupuncture stimulation, and (3) simple tactile stimulation. A licensed acupuncturist delivered all stimulation procedures manually. With their eyes closed, participants were not able to visually distinguish the sham and real acupuncture. The sequence of three different fMRI sessions was randomized and balanced. The same stimulation intensities were used throughout the experiments, and the participants remained in the scanner throughout the entire scan period. A short resting time (less than a minute) was allowed between the each stimulation condition, but head motion was discouraged using a plastic tape.

Since needle-insertion itself does not create significant effects on acupuncture's neural signal,[7] each fMRI session began with a needle (real or sham) in place about a minute prior to the start of the scan (therefore, it is important to note that sensation associated with the insertion of the acupuncture needle did not play any significant role during fMRI session). Auditory beeps were used to relay and pace the stimulation (at 2 Hz) to the acupuncturist using an MR-compatible headset (Avotec, Inc. Jensen Beach, FL). Four stimulation blocks, each 30-s in duration, were interleaved by five 30-s rest periods. This block-based fMRI design was also useful in compensating for possible transitory variation in the intensity of stimulation. During the stimulation periods, participants were asked to passively attend to incoming sensation or listen to the gradient noise in order to prevent possible distraction by imagery, which was often reported by participants in our previous experience. Tactile stimulation, as one of the control conditions in addition to the sham acupuncture, was delivered by gentle brushing of a MR-compatible vonFrey monofilament (much more flexible than an acupuncture needle with a soft end; pressure rating of 133 g/mm^2, Somedic Inc., Horby, Sweden) at 2 Hz against the dorsal aspect of the hand near the *LI*4 area. All stimuli were delivered to an area confined to a less than 3 mm radius from the site of acupuncture. Since the size of the ring was smaller than typical tactile receptive field resolution in the dorsal aspect of the hand,[18] the difference in location of the stimulation was not recognized by the participants.

Psychophysical scores

Numerical analogue scale (NAS) ratings on pain, unpleasantness, and anxiety level[9] were measured using a questionnaire (ranging from 0 to 10, 0 being minimum to 10 being maximum) following each functional session. The participants were freely asked to evaluate their ratings to the best of their ability. Apart from the psychophysical ratings, we examined whether participants were able to distinguish the difference between sham and real acupuncture conditions through a brief interview. The participants were asked to describe their level of confidence ('confident' versus 'not confident') identifying the real acupuncture stimulus. By doing this, we examined the presence of subjective bias toward the real acupuncture versus sham stimulation. Since tactile stimulation was readily distinguishable from the needle stimulations, we did not perform the comparative analysis on the measurement obtained from tactile stimulation. The participants were asked to evaluate the consistency in the intensity of stimulation, whereby all participants reported a consistent level of stimulation.

MR imaging

The experiment was conducted using clinical 3 T MRI scanner (Signa VH, GE Medical Systems). Spin-Echo T1-weighted three-plane images were acquired for anatomical localization, followed by 3D-SPGR (Spoiled Gradient Recalled) sequence (sagittal orientation, TR/TE = 35/7 ms, FA = 45°, 1.5 mm slice thickness, 256 × 192 in-plane matrix, 24 × 24 cm field-of-view (FOV)), which was used to provide high-resolution T1-weighted anatomical data for data registration and cortical inflation procedure.

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Functional data were collected with gradient echo planar imaging sequence (TR/TE = 2000/45 ms and flip angle of 90°), which was acquired with in-plane resolution of 3.13 mm (64 × 64 matrix, 20 × 20 cm FOV) and slice thickness of 3 mm (no slice gap), providing near isotropic voxel geometry. Relatively high spatial resolution for functional data acquisition allows clearer functional definition of the activation around the human Rolandic cortex, facilitating an effective cortical inflation process.[13] Blood-oxygenation-level-dependent (BOLD) signal changes associated with neuronal activation were acquired from 26 axial slices covering the entire cerebrum and the superior aspect of cerebellum. After the acquisition of 10 volumetric data sets to allow for the T1 equilibration, 135 brain volume images were acquired. In order to achieve the timing requirements of the stimulation paradigm, 15 sets of volume images were acquired during each stimulation/rest block. Image quality in the space and time domain was inspected for the presence of any motion artifact.

Data processing

Each image volume was motion-corrected and registered to the image space of the first scan session using SPM2 software. Subsequently, each image volume was normalized to Montreal Neurological Institute (MNI) space based on Talairach coordinates. Normalized images were smoothed with 6 mm full-width-at-half maximum (FWHM) isotropic Gaussian kernel to decrease spatial noise. Group-level activation across the participants was examined using SPM's random effects model.[19] In the first stage, the individual contrast images for the effect of interest were generated by calculating voxel-wise t statistics with respect to the reference waveform designed to conform to the task paradigm using a canonical hemodynamic response function. Confounding effects of fluctuations in the global mean were removed by scaling the signal intensity of each voxel to the global mean for each time point. In the second stage, a one-tail t test was applied to a set of contrast images to determine the group-level activation. Resulting t statistics were normalized to Z-scores, and clusters of significant activation were defined using the joint expected probability distribution of height ($Z > 2.58$; $p < 0.005$) and spatial extent ($p < 0.05$) of the activation.

Since the normalization procedure typically involves spatial interpolation and smoothing, which subsequently confound high-resolution content of the cortical activation, we also processed the data without spatial normalization. In order to do so, the EPI data was coregistered to the individual's high-resolution anatomical images (using SPM), and smoothed with a 3 mm FWHM isotropic Gaussian kernel to reduce spatial noise without significantly affecting the original spatial resolution.

Cortical inflation and anatomical localization

Surface-based analysis and visualization are useful to probe the spatial distribution of activation in the gyral curvature since the inflation algorithm reduces the curvature of gyri and sulci. Since SPM software does not support cortical surface-based analysis, BrainVoyager software package (ver 3.9 Maastricht, The Netherlands), which employs a data analysis approach based on the General-Linear-Model (GLM) similar to SPM, was used in this part of the analysis. First, we interpolated individual participants' functional data onto high-resolution anatomical data. Next, the activations were mapped onto a 3D surface rendering of each individual's brain. Then, after cortical inflation, the anatomical demarcation of detailed boundaries of somatosensory area was readily performed using visual examination. We then applied a rigorous threshold condition, *i.e.*, $p < 10^{-4}$ (uncorrected) for constructing the frequency of activation from each individual. After this individual functional activation map was completed, a group-level analysis was also performed with data normalization to canonical MNI template. Next, we adopted the six anatomical demarcations of the somatosensory areas 6, 4, 3a, 3b, 1, and 2 for each of the three sensory stimulation according to the Moore et al.[13] Finally, we counted the frequency of activation in the observed Brodmann's areas in our 12 participants.

Results

Subjective psychophysical measurement

The post-scan interview revealed that only 3 out of 12 participants were able to distinguish real from sham acupuncture stimulation with confidence. All others were not able to distinguish between the two stimulations, although two participants were able to identify (with much reduced confidence) the real acupuncture based on the different sensory stimulation. The participants' prior knowledge of acupuncture (naïve as 0; prior knowledge as 1) did not bias the ability to dis-

Table 1 The group-averaged results of the stimulation conditions in Talairach coordinate

Anatomy	Acupuncture > rest					Sham acupuncture > rest				Tactile stimulation > rest			
	Side	*x*	*y*	*z*	*Z*-score	*x*	*y*	*z*	*Z*-score	*x*	*y*	*z*	*Z*-score
SI	L	−58	−29	40	3.75	−56	−28	42	3.11	−52	−27	36	4.90
SII	L	−60	−24	20	4.58	−64	−24	20	3.85	−58	−32	20	3.61
	R	56	−24	18	4.56	56	−30	20	3.89	60	−28	18	3.86
Insula	L	−52	−4	6	5.39	−42	−6	−4	3.39	−42	−6	14	3.71
	R	42	−6	16	4.67	38	26	−4	4.44				

Clusters of significant activation were defined using the joint expected probability distribution of height ($Z > 2.58$; $p < 0.005$) and spatial extent ($p < 0.05$) of the activation.

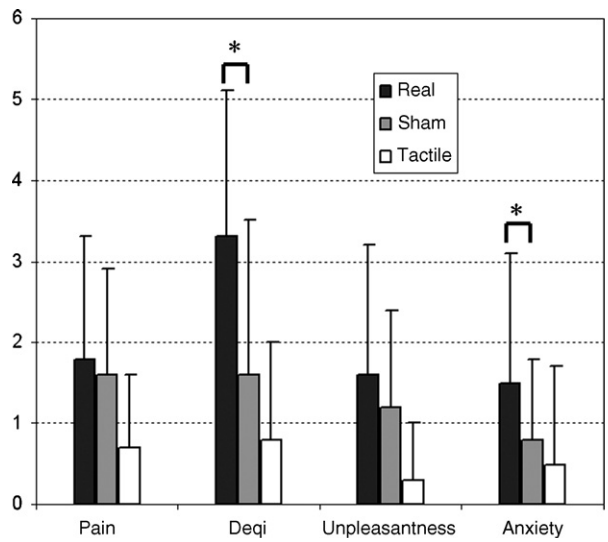

Figure 1 The psychometric measurements for the three different stimulation types across the subjects. When comparing real and sham acupuncture stimulation, *deqi* and *anxiety* ratings have shown significant differences (in asterisk sign, $p < 0.01$).

cern the stimulation type (regression, $p > 0.1$). Fig. 1 shows the psychophysical assessment for the three stimulation conditions. In the examination of the psychophysical assessment between real and sham acupuncture stimulation, only *deqi*-related scores and level of anxiety were elevated during real acupuncture stimulation. Pain intensity and pain unpleasantness were not affected. These data seem to indicate that real and sham stimulation were perceived differentially. The simple tactile stimulation (brushing of a monofilament) was easily distinguished from other stimulation conditions.

Group and individual-level activation

The results from the group analysis in somatosensory areas are summarized in Table 1. *SI* contralateral to the side of stimulation and bilateral *SII* were activated for all stimulation conditions. The insula was activated bilaterally for both real and sham acupuncture stimulation; however, only the contralateral insula was activated during the tactile stimulation using the monofilament. The results from the qualitative evaluation during the three different stimulation conditions (conducted without the spatial smoothing) in terms of the presence of activation (out of 12 individuals) are illustrated in Fig. 2. This qualitative examination reveals that BA1, 2 and 3b were activated across all three conditions. In primary somatosensory areas, however, BA3a, 4 and 6 were more frequently activated during real acupuncture compared to sham acupuncture and tactile stimulation.

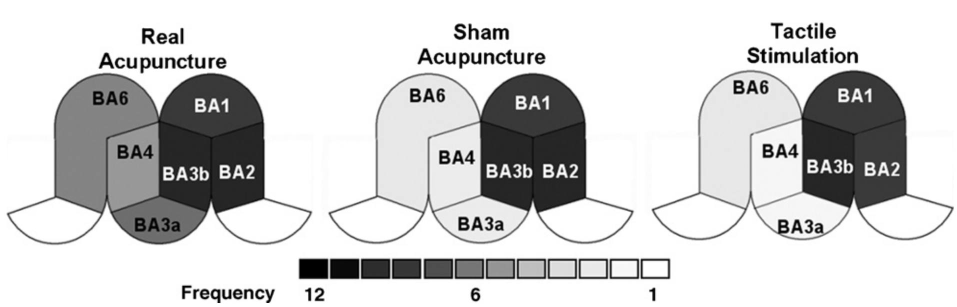

Figure 2 The frequency of detecting activation from 12 individuals, overlaid on the illustration of somatosensory areas (adapted from Moore et al.[13]).

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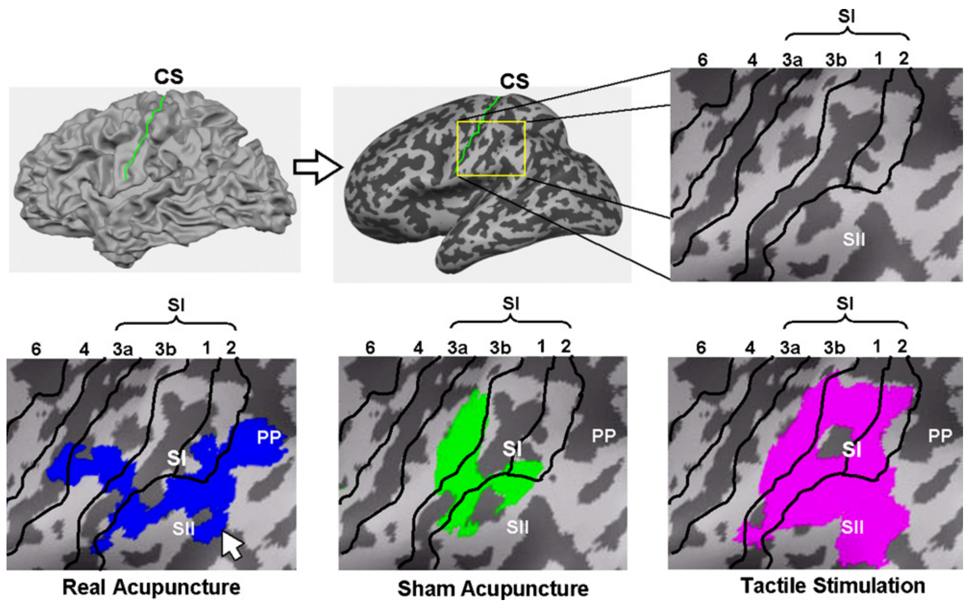

Figure 3 The illustration of inflated cortical areas and the approximated anatomical delineation are shown with group activation map on the inflated cortical surface for different stimulation conditions. The green line indicates the location of the central sulcus. The area with the darker gray represents the inner folding of the gyri (thus deeper sulcal activation). The arrow indicates that extended activation in *SII* area during the real acupuncture stimulation to deeper sulcus of parietal operculum when compared to the sham stimulation. *SI*: primary somatosensory area; *SII*: secondary somatosensory area; PP: posterior parietal areas.

Activation from surface models

The group activation maps on the inflated cortical surface for three different stimulations paradigms are shown in Fig. 3 with an approximate delineation of the regional anatomy. By inflating and coloring cortical sub-regions, we were able to identify the areas that were specifically activated by each stimulation paradigm. Eloquent functional areas in BA3b, 1, and 2, as well as *SII* were activated by all conditions. When compared to the activation map from the sham stimulation, real acupuncture stimulation resulted in activation extended toward BA3a, and posterior parietal areas. In *SII*, real acupuncture resulted in deeper sulcal activation (Fig. 3 in arrow). During sham and control tactile stimulation, activation in BA3a was not evident. These results of activation extending in BA3a support the activation frequency analysis, based on the individual data described above.

Discussion

Our findings demonstrate a differential activation pattern in cortical somatosensory areas that distinguishes the effects of real and sham acupuncture stimulation. Specifically, while all three stimuli elicited activation in primary somatotopic areas 3b, 1 and 2 in all 12 participants, differences between real acupuncture and the two other stimulation conditions were observed in areas BA3a, 4 and 6: more than half of the participants showed activation in these regions, while fewer than 20% of participants showed activation in these areas during the other stimulation conditions. In addition to the activations in BA3a, 4 and 6, surface functional mapping revealed that real acupuncture stimulation resulted in extended activation to posterior parietal (PP) areas (as shown in Fig. 3). In *SII*, we found that real acupuncture resulted in deeper sulcal activation (Fig. 3, in arrow). The subjective psychophysical measurement also indicates that pain intensity and unpleasantness, which are usually observed to be scaled with the intensity of simulation, were not affected by the administration of the real acupuncture condition. Our results indicate that deep tissue stimulation activation of area 3a, and concurrent downstream processing of the sensory stimulation in *SII* and posterior parietal areas may mediate neural responses to acupuncture. This finding supports the hypothesis that acupuncture is mediated by activation of deep proprioceptive neurons in area 3a, unlike in the two control conditions which elicited activation solely in cutaneous responsive neurons in cortical areas 3b, 1 and 2.

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Regarding *SII*, the results seen here are in accordance with those seen in investigations of somatotopy and digit stimulation.[13] Increasing numbers of studies suggest that *SII* is responsive to a broad range of somatosensory stimuli.[20] One specific function of *SII* may be related to the orienting of somatosensory attention,[21] whereby *SII* is more likely than *S1* to be specifically activated when attention to a stimulus is engaged. Our results suggest that the differential effects on *SII* may be a marker of enhanced behavioral relevance or salience of real acupuncture when compared with the two control activations. Such elicitation of attention in the somatosensory system may be an important mechanism by which acupuncture effects pain relief, for example, acupuncture may draw attention away from ongoing pain stimuli. The exact role of posterior parietal areas in the context of acupuncture stimulation is difficult to ascertain: PPA are known to be involved in visual-to-tactile perceptual modulation[22] and may facilitate processing of some of the tactile imagery reported to be associated with the *deqi* sensation[10].

While it has been postulated that widely connected neural networks, involving multiple locations in cortical and sub-cortical areas, may constitute parts of acupuncture's mechanism of action,[7,23] only recently have functional neuroimaging techniques allowed the examination of neural substrates modulated by acupuncture stimulation. Thus, a major strength of this study is its use of detailed functional mapping techniques including a high-field strength magnet and individualized cortical surface inflation technique to assess acupuncture's effects on specific somatosensory areas. This study is the first that we are aware of that uses detailed functional mapping to dissect acupuncture's effects on distinct somatosensory areas.

Although our study revealed interesting features of acupuncture stimulation, it has important limitations. First, even though there seems to be a significant difference of *deqi* rating between real and sham acupuncture, *deqi* was still present in few sham-procedures. Since the sham stimulation involved realistic rotation of the sham needle without the skin penetration, relevant acupuncture points might have been stimulated in some individuals, eliciting *deqi*. In addition, the study was not completely successful in concealing the identity of sham and real stimulation for some participants. While we attempted to render the participants unaware of which stimulation they underwent, a few (three) were able to discern the type of stimulation based on their tactile perceptions, which might have confounded the results with effects of bias/expectation. Regarding the slightly elevated level of anxiety during real acupuncture stimulation, we conjecture that unfamiliar *deqi* feeling during real acupuncture might have raised the anxiety among especially acupuncture-naive individuals.

The differential effects of real and sham acupuncture on the area that encodes deep tissue sensation (area 3a) suggest that the deep needling sensation ('*deqi*') thought to be characteristic of acupuncture treatment may form a part of real acupuncture's neural signal.[24] More broadly, it also reveals a mechanism by which acupuncture specifically elicits changes in cortical dynamics related to processing of deeply felt internal bodily representations. The specificity of somatosensory area 3a findings observed in this study may also be related to acupuncture-driven effects on connective tissue in the periphery: the triggering of such peripheral/central effects[11] may be relevant to the mechanism of action of acupuncture as well as other somatosensory complementary and alternative medicine (CAM) modalities such as the deep tissue aspects of many massage therapies.

Because we invested significant effort in maintaining a consistent intensity of stimulation across participants and conditions, we believe the observed differential activation patterns are not attributable to variations in stimulation intensity. However, future studies should consider adopting a technique such as electrical acupuncture that would provide a method for more precisely validating and making replicable the intensity of stimulation, thereby addressing the question of how stimulus intensity mediates responses in somatosensory areas. Similarly, the use of a more elaborate questionnaire comprised of multiple descriptors and anxiety measures,[25] along with a parametric analysis assessing the degree of association between *deqi* intensity and level of activation should help in dissociating acupuncture's effects on sensory phenomenology from its effects on cortical modulation. A better understanding of the clinical implications of somatosensory cortical modulation of acupuncture would be gained by extending the methods used in this study into a patient population (for example, *LI4* stimulation on chronic pain or migraine headache). By comparing acupuncture's effects on somatosensory cortical areas in chronic pain patients versus healthy individuals, future studies can assess how the mechanism postulated here may be related to the general therapeutic effects of acupuncture.

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