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Correlated Change in Upper Limb Function and Motor Cortex Activation After Verum and Sham Acupuncture in Patients with Chronic Stroke

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ABSTRACT

Background: Acupuncture may improve motor function in patients with chronic hemiparetic stroke, yet the neural mechanisms underlying such an effect are unknown. As part of a sham-controlled, randomized clinical trial testing the efficacy of a 10-week acupuncture protocol in patients with chronic hemiparetic stroke, we examined the relationship between changes in function of the affected upper limb and brain activation using functional magnetic resonance imaging (fMRI).

Methods: Seven (7) chronic hemiparetic stroke patients underwent fMRI and testing of function of the affected upper limb (spasticity and range-of-motion) before and after a 10-week period of verum (N = 4) or sham (N = 3) acupuncture. The correlation between changes in function of the affected upper limb and brain activation after treatment was tested across patients.

Results: We found a significant positive correlation between changes in function of the affected upper limb (spasticity and range of motion) and activation in a region of the ipsilesional motor cortex. Patients treated with verum acupuncture showed a trend toward a greater maximum activation change in this motor cortical area as compared to those treated with sham acupuncture.

Conclusions: Acupuncture may improve function of the affected upper limb in chronic hemiparetic stroke patients by increasing activity in the ipsilesional motor cortex.

INTRODUCTION

Acupuncture may be a useful adjunct to stroke rehabilitation. However, the efficacy of acupuncture to reduce motor impairments in patients who have had strokes is equivocal.[1,2] Furthermore, the neural mechanisms that may underlie a beneficial effect of acupuncture in patients with stroke are not known.[2]

A sham-controlled, randomized clinical trial (RCT) was conducted to test the efficacy of acupuncture to improve up-

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per limb function in patients with chronic hemiparetic stroke.[3] It was found that among patients who complied with the protocol, spasticity and range of motion of the affected upper limb improved in those treated with verum acupuncture as compared to sham acupuncture. In a subset of patients, the potential neural effect of acupuncture was evaluated using functional magnetic resonance imaging (fMRI). Previous fMRI studies in patients with stroke have shown that motor recovery is associated with reorganization of brain activation within the motor network,[4] including increased activation in the motor cortex of the lesioned hemisphere.[5,6] The current study tested the hypothesis that gains in upper limb function (spasticity and range of motion) after acupuncture correlate with increased activation in the ipsilesional motor cortex. Recent studies have suggested that acupuncture's efficacy in treating painful conditions may be caused, in part, by a physiologic placebo effect.[7–9] Therefore, this study also examined whether changes in brain activation differed between patients treated with verum versus sham acupuncture.

PATIENTS AND METHODS

The RCT enrolled patients with moderate chronic hemiparesis caused by a single stroke.[3] The first 8 of these patients who (1) did not exhibit resistance to passive movement of the metacarpophalangeal joint of the second digit (D2) of the affected hand; (2) had at least minimal perception of passive movement of the affected D2 (sensation score $\geq$1, with 0 = none, 1 = minimal, 2 = moderate, 3 = good); and (3) agreed to undergo MRI also enrolled in the fMRI substudy of the RCT. The 8 patients were randomized into verum and sham acupuncture groups. However, 1 of the 8 patients withdrew participation prior to completion, leaving the verum group with 4 patients and the sham group with 3 patients (Table 1). All data collected from the eighth patient were excluded from analysis. All 7 patients had a lesion that spared the hand region of the primary sensorimotor cortex.[10] Treatment was based on the Traditional Chinese Medicine style of acupuncture, and was administered twice weekly for 10 weeks. The protocol involved manual acupuncture to body and scalp points, and electroacupuncture to body points. Sham acupuncture involved a nonpenetrating, retractable needle[11] and a disconnected electrical stimulator. Testing of affected upper limb function and MRI sessions, when applicable, were conducted at baseline and 12 weeks later. Patients and outcome assessors were blinded to group assignment. The outcome of patient blinding was assessed after 2 weeks of treatment and again 12 weeks later, using methods described in detail previously.[3]

MR image acquisition

MRI was conducted using a 3T Siemens Trio system (Siemens Medical Solutions, Erlangen, Germany) and a transmitter/receiver head coil. Patients were fit with a bite bar to limit head motion, and splints to immobilize the forearms, wrists, and hands. In addition, the D2 interphalangeal joints of the affected and unaffected hands were splinted in extension.

High-resolution T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) images and T2-weighted turbo spin-echo structural images were collected. Functional images were acquired using a T2*-weighted gradient-echo, echo planar imaging sequence (echo time/repetition time = 1500/30 ms; flip angle = 90°; field of view = 200 $\times$ 200 mm; matrix size = 64 $\times$ 64; slice thickness = 5 mm; interslice gap = 1 mm; number of slices = 24; acquisitions/slice = 182). Functional images were collected while an investigator alternated between displacing a D2 splint to move the metacarpophalangeal joint passively (6 $\times$ 21 seconds; resting position to 30° extension; alternately 0.75/1.5 Hz) and resting (7 $\times$ 21 seconds). Patients were trained to close

TABLE 1. PATIENT CHARACTERISTICS

Patient no.	*Group*	*Gender*	*Age (yr)*	*Stroke*				*D2 sensation (score)*
				Side	*Location*	*Type*	*Chronicity (yr)*	
1	V	M	68	L	CR, BG, IN, TP	I	1.0	3
2	V	M	75	L	T	I	7.8	1
3	V	F	28	R	FR, CR	H	2.5	3
4	V	M	80	L	CR, PLIC, T	I	3.4	2
5	S	F	58	R	CR, ALIC, PLIC, BG, IN, TP	I	10.2	3
6	S	M	42	L	MCP	I	3.4	2
7	S	M	48	L	T	H	4.1	2
Summary	4V/3S	5M/2F	57 ± 19	5L/2R		5I/2H	4.6 ± 3.2	2.3 ± 0.8

V, verum acupuncture; S, sham acupuncture; M, male; F, female; L, left; R, right; CR, corona radiata; BG, basal ganglia; IN, insular cortex; TP, temporal lobe; T, thalamus; FR, frontal lobe; PLIC, posterior limb internal capsule; ALIC, anterior limb internal capsule; MCP, middle cerebellar peduncle; I, ischemic; H, hemorrhagic. Summary values are mean ± standard deviation.

their eyes, relax their entire bodies, attend to the passive movement, and to neither assist nor resist the passive movement during fMRI. Four sets of functional images were collected per patient (2 × affected D2 passive movement; 2 × unaffected D2 passive movement).

Data analysis

Given the intent to evaluate the relationship between changes in upper limb function and brain activation, a composite change score was computed in upper limb function for each of the 7 patients based on those measures that showed significant ($p < 0.01$, multiple linear regression analysis) between-group differences in the RCT.[3] Accordingly, upper limb function change scores were based on wrist spasticity using the Modified Ashworth Scale (scale: 0–4),[12] and active-assisted range of motion (in degrees) of shoulder abduction and adduction, and wrist flexion, extension, and ulnar deviation (radial deviation was excluded because of missing data). For each patient, change (12-week minus baseline testing session) in these measures was converted to percent change (based on full scale), then averaged. Composite change scores of upper limb function were used to test for between-group differences using the Mann-Whitney test (alpha set to 0.05), and to correlate against changes in brain activation.

Images were analyzed using Freesurfer* and AFNI/SUMA† software. Lesion location was determined from the T2-weighted images. To perform group-level image analyses, images from patients with a right-sided stroke were flipped about the midsagittal plane, thereby lateralizing the lesion to the left hemisphere in all patients. A model of the each patient's cortical surface was generated using the T1-weighted images.[13] Each cortical surface was spatially normalized into a spherical, node-based coordinate system.[14] Functional images from each patient were co-registered with their T1-weighted images, motion-corrected, signal intensity-normalized, and spatially smoothed using a three-dimensional Gaussian kernel (full-width-at-half-maximum [FWHM] = 2 mm).

To estimate group-average activation responses to unilateral passive movement of D2, functional time-series were mapped to the normalized cortical surface, then smoothed using a two-dimensional Gaussian kernel (FWHM = 2 mm). A general linear model that included a baseline drift term and a canonical stimulus input function was fit at each cortical surface node, with subject regarded as a fixed-effect. Average activation maps were evaluated at a significance level of $p < 10^{-3}$, corrected for multiple comparisons by thresholding individual nodes to $p < 10^{-4}$ and imposing a minimum cluster extent of 17 mm,[2] based on a method described previously.[15,16]

To test the hypothesis that changes in upper limb function and motor cortex activation correlate, we performed the following steps. Each patient's volumetric functional data were concatenated. A general linear test was conducted to estimate the difference in the fMRI signal at the 12-week session versus the baseline session. The model included baseline linear drift terms, motion-correction parameters, and a canonical stimulus input function. The resulting difference maps were spatially normalized, then smoothed (FWHM = 2 mm). Finally, a linear regression model was fit at each cortical surface node to estimate the correlation between changes in activation and upper limb function across the patients who received either verum or sham acupuncture. Regression maps were evaluated at a corrected significance level of $p < 0.05$ (individual node threshold $p < 0.01$, minimum cluster extent = 45 mm^2).[15,16] We further interrogated cortical areas exhibiting a significant correlation between change in upper limb function and activation by examining the relationship between upper limb function change and maximum activation change using Pearson's correlation coefficient, and the between-group difference in maximum activation change using the Mann-Whitney test with alpha set to 0.05.

*Available at http://surfer.nmr.mgh.harvard.edu
†Available at http://afni.nimh.nih.gov

RESULTS

The success of blinding the 7 patients of this fMRI substudy to group assignment was similar to that reported in the larger group of patients who participated in the RCT.[3] After 2 weeks of treatment, only 1 of the 7 patients (14%) correctly guessed group assignment (compared to 28% of patients in the RCT). After completion of the treatment, 12 weeks later, only 2 of the 7 patients (29%) correctly guessed assignment (compared to 35% of patients in the RCT). These results suggest successful blinding of the patients enrolled in the fMRI substudy of the RCT.

The 7 patients showed a range of change in function of the affected upper limb, based on measures of spasticity and range of motion, after the acupuncture protocol relative to baseline (−29% to 19%). Grubb's test[17] for outliers revealed that the −29% upper limb function change exhibited by 1 patient (#5) was an outlying value. Among the remaining 6 patients, the range of upper limb function change was 1% to 19%. There was a trend toward greater improvements in upper limb function in patients treated with verum acupuncture compared to sham acupuncture (rank sum verum = 21, sham = 7; $p = 0.077$, Mann-Whitney test).

The group-average activation response to passive movement of the affected D2 at baseline was most marked in the hand region of the primary sensorimotor cortex[10] contralateral (i.e., ipsilesional) to the stimulation (Fig. 1). Activation was also observed in opercular regions bilaterally, including the secondary somatosensory cortex. This regional pattern of activation was also observed during passive movement of the unaffected D2 at baseline, and was largely unchanged during passive movement of the either D2 after the acupuncture protocol (data not shown).

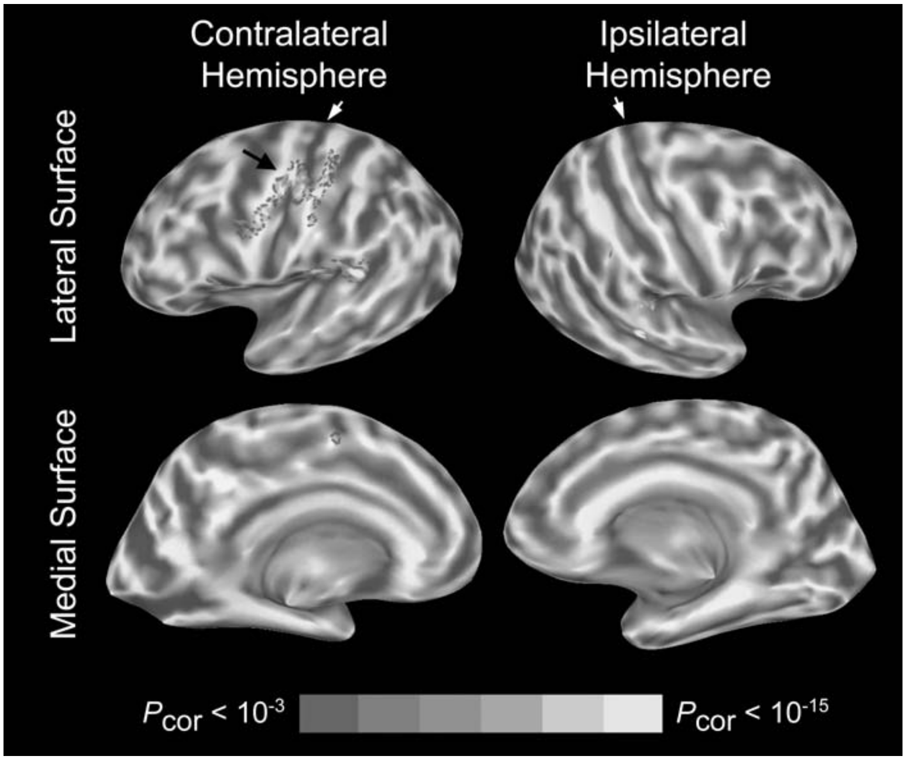

FIG. 1. Group-average cortical activation before acupuncture. Group-average statistical activation maps ($p < 10^{-3}$, corrected) during passive movement of the affected D2 at the baseline magnetic resonance imaging session. Activation maps are displayed on a representative, inflated cortical surface model. Dark gray areas represent sulci; light gray areas represent gyri. White arrows identify the central sulcus. Black arrow identifies the hand region of the motor cortex. Please see color version of this figure online at www.liebertonline.com/acm

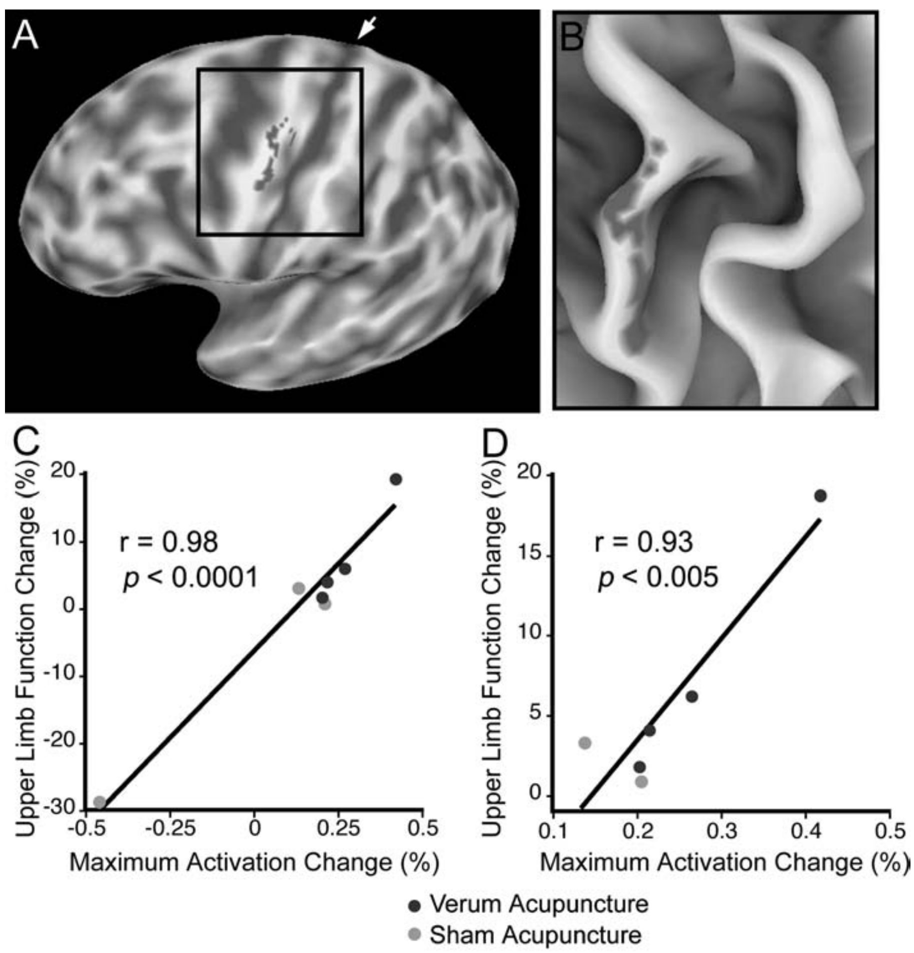

FIG. 2. Correlation between changes in upper limb function and cortical activation after an acupuncture protocol. **A.** Cortical area exhibiting a significant ($p < 0.05$, corrected) correlation between changes in upper limb function and activation after the acupuncture protocol, displayed on an inflated cortical surface model. The area is in the hand region of the contralateral (ipsilesional) motor cortex. **B.** Enlargement of region outlined in (A) displayed on the folded cortical surface model. **C.** Correlation between change in upper limb function and maximum activation change in the motor cortical region shown in (A) and (B), using data from all 7 patients. **D.** Same as (C), except excluding data from patient 5 (based on outlying upper limb function change value). Please see color version of this figure online at www.liebertonline.com/acm

Regression analysis revealed that after the 10-week acupuncture protocol, change in upper limb function significantly ($p < 0.05$, corrected) and positively correlated with change in activation within a region of the contralateral (ipsilesional) motor cortex during passive movement of the affected D2 (Fig. 2). Of note, because the regression analysis involved data from all the patients, this result does not distinguish effects of verum relative to sham acupuncture on upper limb function or activation. Further interrogation verified a significant correlation between upper limb function change and maximum activation change in this motor cortical area when data from patient 5 was included (r = 0.98, $p < 0.0001$, Pearson's correlation) or removed (r = 0.93, $p < 0.005$). Patients treated with verum acupuncture showed a trend toward a greater maximum activation change in this motor cortical area compared to those treated with sham acupuncture (rank sum verum = 21, sham = 7; $p = 0.077$, Mann-Whitney test). There was no significant correlation between change in upper limb function and activation during passive movement of the unaffected D2.

DISCUSSION

The main finding of this fMRI study was a significant positive correlation between changes in function of the affected upper limb and activation in the contralateral (i.e., ipsilesional) motor cortex after an acupuncture protocol in patients with chronic hemiparetic stroke. Previous brain imaging studies have shown that acupuncture increases activity in motor cortices in healthy adults[18] and stroke patients.[19] To our knowledge, this is the first report of an acupuncture protocol modifying motor cortex activity in relation to upper limb function in patients with hemiparetic stroke. After the acupuncture protocol, all but 1 patient showed improvements in a composite measure of spasticity and range of motion that paralleled increases in activation in the ipsilesional motor cortex. It is unclear why one patient (#5) experienced reduced upper limb function and ipsilesional motor cortex activation after sham acupuncture. Although the lesion in this patient was more extensive than those in the other patients, the level of upper limb function (spasticity and range of motion) in this patient was within the range of the other patients. In the fMRI study and the larger RCT,[3] the clinical benefit of acupuncture on upper limb function of the patients was generally modest. However, this modest beneficial effect appears linked to increased activity in the ipsilesional motor cortex. This finding is consistent with prior brain mapping studies in stroke patients demonstrating increased ipsilesional motor cortex activity associated with gains in motor function after motor rehabilitation.[6,20,21] The precise mechanism underlying this effect of acupuncture is unknown. However, it is possible that by increasing ipsilesional motor cortex activity, acupuncture helps restore activity along spared descending motor pathways, thereby improving cortical modulation of lower motor neuron excitability involved in spasticity and range of motion.

Within the motor cortical area exhibiting a significant correlation between changes in upper limb function and activation, we found that the patients treated with verum acupuncture showed a trend toward greater increases in activation as compared to those treated with sham acupuncture. The lack of a statistically significant difference between groups may have been caused by low statistical power. It is also possible that the lack of a statistically significant between-group effect reflects little difference in the physiologic effects of verum versus sham acupuncture, as has been suggested by some studies examining the efficacy of acupuncture in treating painful conditions.[7–9] The statistical trend we observed, however, tentatively suggests that verum acupuncture may more effectively facilitate increases in motor cortex activity as compared to sham acupuncture in patients with chronic hemiparetic stroke. This suggestion is consistent with the recent finding that acupuncture needling, but not sham needling, increased motor cortex excitability in healthy adults.[22]

CONCLUSIONS

The results of this pilot fMRI study suggest that acupuncture therapy in patients with chronic hemiparetic stroke may modestly improve upper limb function (spasticity and range of motion) by increasing ipsilesional motor cortex activity. Further studies that involve larger sample sizes are needed to determine whether verum acupuncture has a differential effect on brain activity as compared to sham acupuncture. Such studies may ultimately lead to the scientifically based use of acupuncture as an adjunct to stroke rehabilitation.

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