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Spatiotemporal Mapping the Neural Correlates of Acupuncture with MEG

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Abstract

Acupuncture is an ancient Eastern healing modality with putative therapeutic applications. Unfortunately, little is known about the central mechanisms by which acupuncture may exert its effects. In this study, 15 healthy subjects were evaluated with magnetoencephalography (MEG) to map the location and timing of brain activity during low-frequency electroacupuncture (EA) and mechanical, noninsertive, sham acupuncture (SA) given at acupoint PC-6. Both EA and SA evoked brain responses that localized to contralateral primary somatosensory (SI) cortex. However, initial responses for EA peaked slightly earlier than those for SA and were located inferiorly within SI. Average equivalent current dipole strength was stronger (particularly at latencies >60 ms) for SA. These spatiotemporal differences between activations elicited by EA and SA are likely attributable to stimulus modality (electrical versus mechanical) and differences in the underlying somatosensory fibers transmitting these signals. The present data confirm that acupuncture modulates activity within somatosensory cortex, providing support for previous studies that suggest that the therapeutic effects of acupuncture are linked to SI modulation. Thus, MEG provides excellent spatiotemporal characterization of the somatosensory component of acupuncture, and future studies can contrast derived brain response parameters in healthy controls with those found in a diseased state.

Introduction

Neuroimaging techniques such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) allow us to noninvasively monitor the effects of acupuncture in the human brain. Recent fMRI data demonstrate that acupuncture modulates a distributed network of cortical, subcortical/limbic and brainstem regions.[1] However, fMRI only measures hemodynamic changes that are slow (>1 second) and cannot directly track neuronal electrical activity following an acupuncture stimulus on a millisecond timescale. Fortunately, both EEG and MEG may be used to reveal the time course of these rapid somatosensory responses. Although there are no previously published data utilizing MEG to evaluate the effects of acupuncture on brain activity, EEG has been used extensively to study the effects of manual acupuncture (MA) and electroacupuncture (EA) on somatosensory evoked potentials* (SEPs) to both nonpainful and painful stimuli.

EEG studies investigating the effects of MA on nonpainful SEPs evoked by stimulation of leg acupoints found that 20 minutes of MA decreased amplitude of early latency SEPs, suggesting that acupuncture may modulate activity within spinal nerves and/or primary somatosensory cortex.[2] Yet, similar studies did not find early modulation with arm/hand[3,4] or facial acupoint stimulation.[5] Studies utilizing EA have less methodological variability associated with needling than MA and have demonstrated that the time course of SEPs generated by EA given at hand acupoints are similar to median nerve SEPs.[6,7] Furthermore, to help determine whether acupuncture modulates early sensory/discriminative or late cognitive/affective components of SEPs, previous studies have combined administration of acupuncture and anesthetics. One study argued that acupuncture modulates attentional mechanisms as it decreased amplitude of the P250 pain component.[8] However, modulation of pain SEPs may occur even when subjects are unconscious under anesthesia,[9] and although confounding effects may occur when acupuncture is combined with some anesthetics,[10]

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*Somatosensory EEG and MEG studies often utilize paradigms in which sensory stimuli are given repeatedly. Trials are averaged so that evoked brain responses that are time locked to the stimulus event become visible against background noise. For EEG, these responses are called somatosensory evoked potentials (SEPs) and for MEG they are called somatosensory evoked fields (SEFs).

other data found no effect of acupuncture on pain regardless of whether anesthesia is given prior to or following EA,[11] but again the results varied. Finally, the time courses of EA SEPs and their effects on both nonpainful and painful sensory stimuli have been found to be highly dependent on the interstimulus interval used, with short intervals (<2 seconds), commonly used in clinical settings, resulting in an overlap of long-latency components,[6,12,13] thus making it difficult to interpret many of these studies.

Collectively, studies of acupuncture effects on nonpainful and painful SEPs have produced mixed results and are confounded by the need to use long (>2 second, which is uncommon for clinical EA) interstimulus intervals when multiple stimuli are used. It is also unclear whether acupuncture acts similarly on experimental pain as on chronic pain, and difficulties interpreting the effects of anesthetics combined with EA demonstrate that their concurrent use provides little additional information regarding the neural mechanisms of acupuncture. Finally, although previous EEG studies provide some useful information regarding the timing of acupuncture effects, all of them lack information regarding the anatomical location of the underlying brain activity. In the present study, we used anatomically constrained MEG to spatiotemporally map somatosensory evoked brain response to EA and sham acupuncture (SA) given at a clinically relevant frequency (2 Hz) without confounding measurements with other somatosensory/pain stimuli or the use of anesthetics. To further mimic clinical intervention procedures, acupuncture stimulation was given continuously for 15 minutes while MEG was recorded. To our knowledge, this is the first MEG investigation of acupuncture, thus providing novel insight into the spatiotemporal dynamics of neural responses underlying this healing modality.

Methods

Subjects and experimental paradigm

Data were collected for 15 healthy, right-handed[14] adults, 20–54 years of age (mean 28 ± 9 years). Subjects were recruited via fliers/newsletters adhering to Massachusetts General Hospital (MGH) guidelines for distribution at neighboring academic institutions and hospitals. Subjects were screened to assure their safety and compatibility for MEG and MRI recordings. All participants gave written informed consent, and the study was approved by the Human Research Committee at MGH.

The experiment consisted of five runs (three rest runs and two acupuncture runs; Fig. 1A) during which subjects were seated within the MEG system and instructed to fixate on a centrally presented "+" sign. During each 10-minute rest run (i.e., Run 1, Run 3, Run 5) there was no acupuncture intervention and subjects were required to sit quietly. Rest runs were used in order to reduce residual sensations before the second acupuncture run. Data were recorded during rest runs to allow for the future evaluation of possible changes in heart rate variability and brain activity before versus after stimulation. The order of EA and SA runs was randomized across subjects. Both EA and SA consisted of 15 minutes of continuous low-frequency (2-Hz) stimulation given on the left medial forearm at acupoint PC-6 (pericardium-6, neiguan). All acupuncture was performed by the same licensed (and experienced) acupuncturist. Subjects wore earplugs throughout the experiment to attenuate any sounds heard from outside the MEG room or from stimulation equipment.

In the current studies, we employed stimulation at PC-6, which has traditionally been used in the treatment of cardiovascular diseases and nausea.[15] Importantly, because MEG is biased toward superficial brain activity, primary somatosensory (SI) responses for points on the forearm are more confidently mapped with MEG than those of the leg (e.g., ST-36) which are located medially in the brain.[16]

Electroacupuncture procedures

During both SA and EA subjects wore a plastic brace (Fig. 1B, C) on their forearm to prevent potential fist clenching and excessive hand movement. A rectangular opening over the medial forearm provided access to acupoints. Following needle insertion and initial manipulation (to elicit *de qi* sensation), electrical current was delivered. Current amplitude was set to the level at which subjects indicated feeling a "strong but not painful" sensation. Current was delivered as a monophasic rectangular, constant-current pulse (pulse width: 0.2 ms at 2 Hz) using a GRASS stimulator (S88 Dual Output Square Pulse Stimulator, Grass Telefactor, West Warwick, RI).

Sham acupuncture procedures

Our sham acupuncture was chosen to simulate a typical, mechanical, noninsertive stimulation but be given with millisecond temporal precision needed for MEG studies. Thus, the plastic brace was equipped with a piezo-electric cantilever beam (Piezo Bender Q-503B, Piezo Systems, Cambridge, MA). The piezo was positioned over the acupoint for each subject prior to SA. The device was battery powered and controlled with National Instruments (NI) Labview program in combination with the 6100 DAQ card (NI) located in a laptop with Labview software. The digital signal was converted with a D/A converter and amplified (Low Cost Linear Amplifier, Piezo Systems Inc.) prior to reaching the piezo. The stimulus waveform was a single lobe from a 100-Hz half-sine wave (pulse width 5 ms).

To promote adequate blinding, participants were told they would receive "two different types" of acupuncture. Subjects were prevented from viewing all acupuncture insertion and stimulation procedures through the use of an opaque screen. Subjects were intentionally shown wrapped needles and cotton-tipped swabs during both runs. Importantly, in order to most closely match active stimulation in the EA run, the SA procedure was twofold:

1. *Sham insertion:* As with EA, subjects were first palpated near the acupoint to mimic acupoint localization. Insertion was then simulated using a wooden toothpick positioned on the acupoint with a guide tube.[17] The toothpick was manipulated and subjects were asked what sensations they felt and if there was any pain. During this time, the piezo-stimulator tip was lowered onto the acupoint.

2. *Stimulation:* The stimulator-tip touched the skin over the acupoint and stimulation consisted of a 2-Hz mechanical pecking to mimic EA frequency. Stimulation was set to a level at which subjects indicated feeling a "strong" (not painful) sensation.

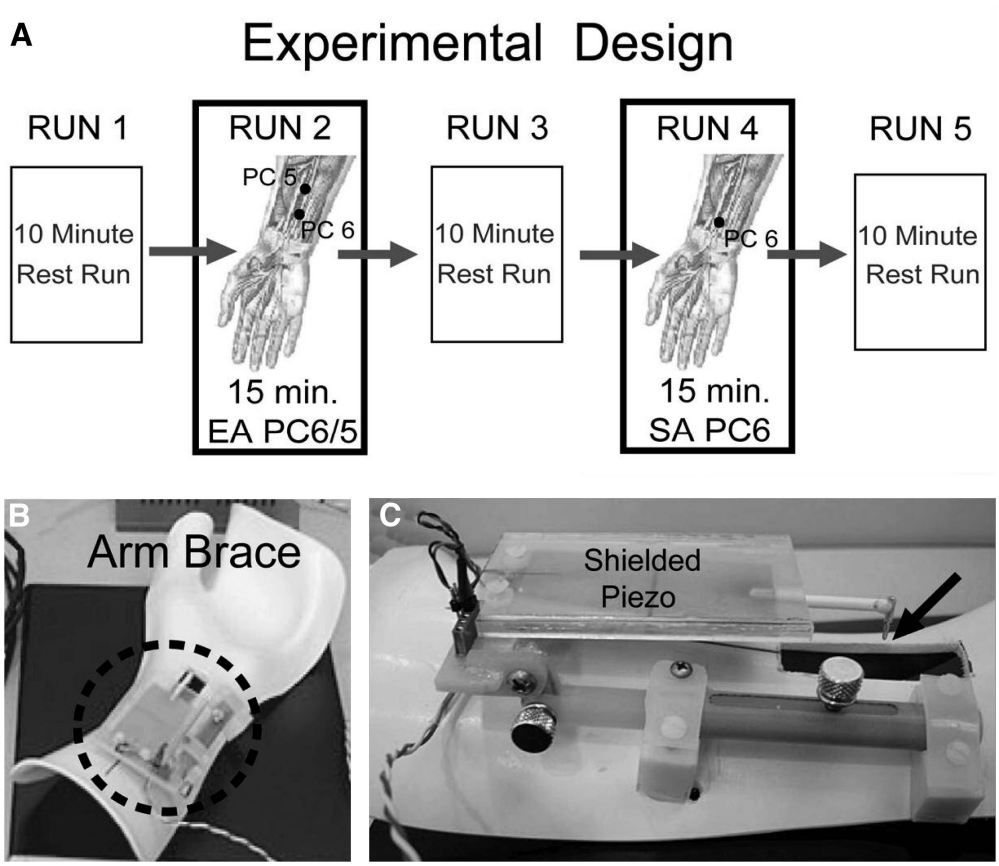

FIG. 1. Experimental design and the arm brace. **A.** Each magnetoencephalography (MEG) scan consisted of three rest runs and two acupuncture runs (electroacupuncture [EA] and sham acupuncture [SA]). Acupuncture run order was randomized across subjects and consisted of 15 minutes of continuous low-frequency (2 Hz) stimulation. During each 10-minute rest run, MEG was recorded while subjects sat quietly. **B.** During EA and SA, subjects wore an MEG-compatible arm brace to reduce hand movement. The brace was equipped with a piezo-driven stimulator (dashed black circle). **C.** An enlarged image of the piezo-driven stimulator. The stimulator was anchored to the arm but adjustable so that the stimulation tip (black arrow) could be placed at the correct position on the skin surface. A rectangular opening in the brace allowed access to underlying acupoints.

A tactile SA control was chosen over noninvasive electrical stimulation for multiple reasons. First, we felt that surface electrical stimulation would not qualify as sham but instead approximate transcutaneous electrical acupoint stimulation (TEAS) acupuncture. Second, the use of surface electrodes does not guarantee that deep nerve or muscle fiber stimulation would not occur (as expected with needles). Finally, we felt that noninvasive sham could be used as a viable control if insertion was emulated and the mechanical stimulation was at the same frequency as the EA. A similar "tapping" procedure has been conducted manually in acupuncture fMRI studies.[18] Manual acupuncture and manual sham procedures are adequate in fMRI studies that measure brain activity in seconds; however, they are not appropriate for MEG studies evaluating SEFs, which require precision timing (millisecond accuracy) of stimuli, as provided by EA and our piezo-driven SA device.

Psychophysical data collection and analysis. Prior to each experiment, subjects were given a questionnaire, aimed at assessing their somatosensory expectancy for acupuncture, consisting of a list of 13 words (taken from the survey below) and asked:

> Which (if any) of the following sensations do you *expect* that you will feel during acupuncture? Give your answers as "Yes" or "No." Briefly state what knowledge you are basing these expectations on (i.e., book, friends, Web, etc.).

Following the MEG recording session, subjects rated the intensity of sensations they felt during each acupuncture run. Subjects were presented with a 10-point visual analog scale, with 0 indicating no sensation and 10 indicating the strongest sensation possible. Responses were acquired with a laptop and Labview Software. Subjects were asked to rate the extent to which they felt sensations commonly associated with the experience of *de qi* (i.e., aching, soreness, pressure, heaviness, fullness, warmth, cool, numbness, tingling, dull pain, etc.). These were the same words used in the pre-scan expectancy questionnaire. Subjects were asked to assess the extent of sharp pain and the extent of "spreading" that may have occurred for any of the listed sensations. In order to quantify the total amplitude of *de qi* experienced, we used the MGH Acupuncture Sensation Scale Index (MASS-Index), which aims to give weight to sensation severity along with

multiplicity or variability.[19] In other words, this index gives weighting to the amplitude score for any particular sensation, as well as the number of different sensations chosen by the subject. For every experiment run, one can calculate the MASS index as follows:

$$\text{MASS Index} = \frac{\sum_{i=1}^{n} (1/2)^i S_i}{1 - (1/2)^n}$$

where S_1 is the highest intensity score for any *de qi* sensation, S_2 is the second highest intensity score for a different sensation, S_3 is the third highest, and so on. Frequency counts of different sensations were also compared between different groups with a χ^2 test, significant at $\alpha < 0.05$.

Following the MEG recording session, subjects were given a questionnaire to assess which stimulation type (verum or sham acupuncture) best matched their initial expectation of what acupuncture should feel like. Subjects were asked:

> During the session, you experienced different types of acupuncture, which may have produced different sensations. Which of the different types of acupuncture (1st or 2nd acupuncture run) most closely matched your initial expectations of what acupuncture would feel like? Briefly explain why. Refer to your initial questionnaire if necessary.

Methods for MEG and structural MRI data collection: MEG data collection. MEG signals were recorded with a 306-channel Vectorview Biomagnetometer (Elekta Neuromag Oy, Helsinki, Finland). The head position was monitored during the measurement using head position indicator coils (HPI). The subject's head and the HPI coils were digitized using a Polhemus (Colchester, VT) FastTrak digitizer to allow for accurate alignment of the MEG sensor array with the subject's MRI scan. The acquisition bandwidth was 0–400 Hz with a 1200-Hz digitization rate. The subject's electrocardiogram (ECG) and electro-oculogram (EOG) were recorded simultaneously to control and if necessary remove influence from physiologic noise sources such as heartbeat, eye blinks, and eye saccading.

Methods for MEG and structural MRI data collection: High-resolution, structural MRI data collection. Individual MRI scans are necessary to assure accurate localization of MEG signals. Each subject underwent an MRI scan that was co-registered with the MEG data. The anatomical MRI was used for creation of boundary element models and visualization of the cortical surface anatomy. Each subject was scanned in a Siemens Avanto 1.5-Tesla MRI (Siemens Medical, Erlangen, Germany). Two high-resolution MPRAGE (256×256 matrix [256-mm field of view (FOV)],128 slices, 1.33-mm slice thickness, echo time [TE] = 3.39 ms, repetition time [TR] = 2530 ms, inversion time [TI] = 1100 ms, flip = 7°) images (averaged offline) and a multi-echo 3D-fast low-angle shot scan (256×256 matrix [256-mm FOV], 128 slices, 1.33-mm slice thickness, TE = 5.91, TR = 20 ms, 3 echoes, echo spacing = 100 μs, flip = 5°) were acquired.

MEG data analysis: MEG equivalent current dipole (ECD) analysis. Many MEG studies of somatosensory processing utilize single dipole analysis with the assumption that there is only a single or relatively few sources of activity. In general, ECD fitting is performed through least-squares fitting for the MEG sensor data to potential source locations within either a spherical or realistic head model, the later of which is constructed from individual subject MRIs.[16] In the current study, we utilized the XFit software (Elekta Neuromag Oy, Helsinki, Finland) with a spherically symmetric head model fitted to the shape of the inner skull surface. The distance between EA and SA ECDs was computed as the Euclidean distance between the corresponding dipole locations. For final visualization, the ECD locations in each subject were projected onto their inflated cortical surfaces.

MEG data analysis: MEG distributed source estimates. To confirm the results of ECD analysis, as well as to readily visualize potential simultaneous activity within multiple locations, distributed source modeling was employed. A minimum norm estimate[20] was used to solve the ill-posed inverse problem of assigning time courses measured with relatively few channels (306) to many source locations (~6000). To further constrain the inverse solution, we made the assumption that the generators of the measured field be located in the cortical mantle and that the currents producing the MEG and EEG signals were approximately orthogonal to the cortical surface.[21]

The geometry of the cortical surface employed as a constraint was generated by the FreeSurfer[22,23] software and used each subject's MRI scan (reconstructed from high-resolution MPRAGE images). For purposes of intersubject averaging, the reconstructed surface for each subject was morphed into an average spherical representation, optimally aligning sulcal and gyral features across subjects while minimizing metric distortions and shear,[24] and MEG response amplitude was mapped onto an average sulcal–gyral pattern. For the MEG forward calculation, we employed the boundary element method (BEM), which assumes the head is composed of arbitrarily shaped compartments with constant electrical conductivity. We employed in-house-developed software for extracting the surfaces separating the relevant compartments (scalp, skull, and brain) from anatomical MRI data. The BEM was then used for calculating the signal expected at each MEG sensor, for each dipole location.[25,26]

To estimate the time courses of cortical response, we used the noise-normalized, anatomically constrained linear estimation approach described by Dale et al.[27] This approach is similar to the generalized least-squares or weighted minimum norm solution,[20] except that the modeled sources were constrained to lie in the cortical surface,[28] and the estimate was normalized for noise sensitivity such that source signal-to-noise ratio rather than current dipole moment was mapped.[27] The noise normalization also has the effect of greatly reducing the variation in the point-spread function between locations.[29] This approach provides statistical parametric maps of cortical response, similar to the statistical maps typically generated using fMRI, or positron emission tomography data, but with a temporal resolution of 5 ms or less.

The maps were calculated every 5 ms for every condition and every individual. The square roots of these values were then averaged on the cortical surface across individuals after aligning their sulcal–gyral patterns. The square root was used in order to de-emphasize outliers and ensure that the

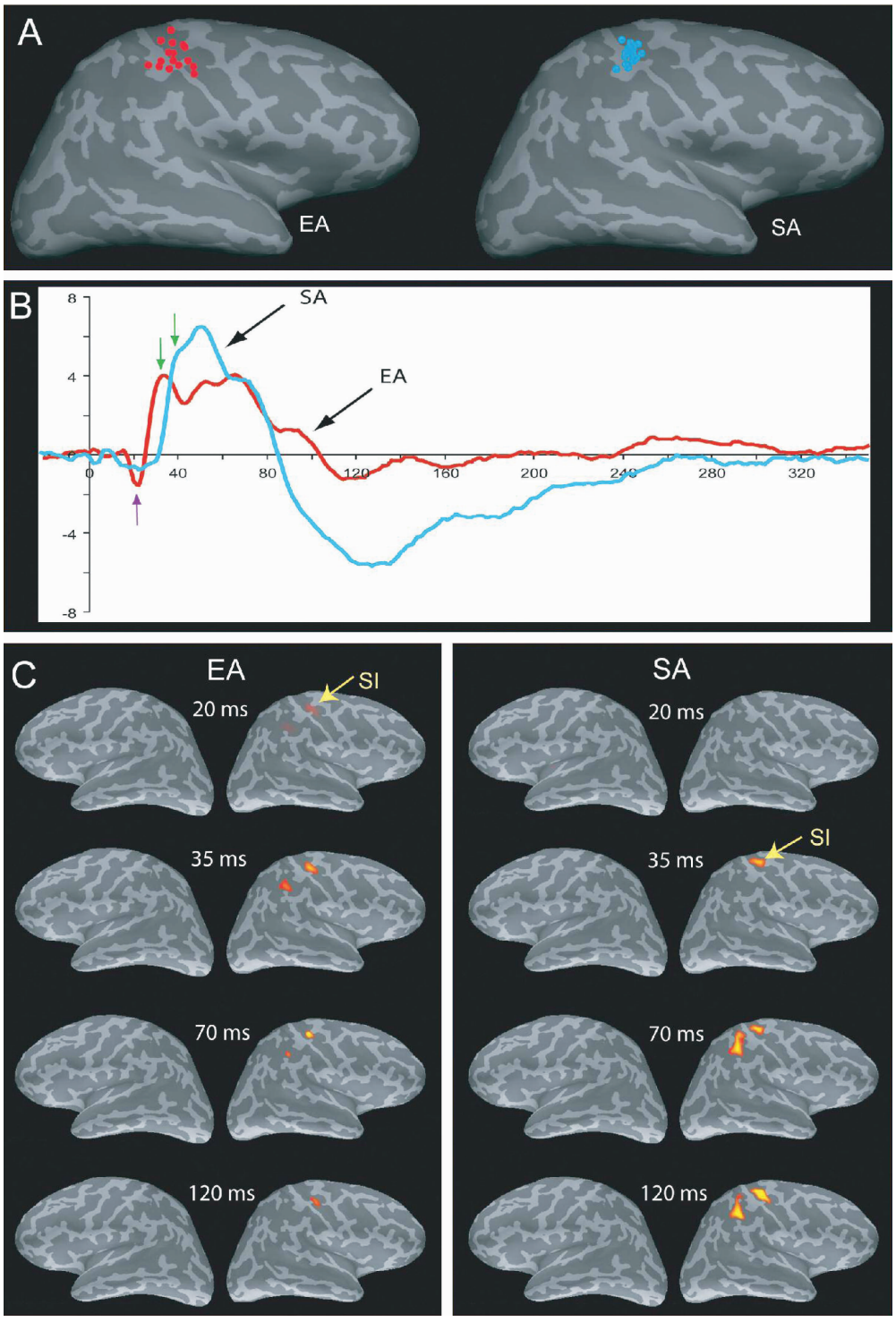

FIG. 2. Equivalent current dipole (ECD) and distributed source analysis of electroacupuncture (EA) and sham acupuncture (SA) conditions. **A.** ECD localization for 15 subjects demonstrated that sources for both EA (red) and SA (blue) map proximally to one another along the contralateral somatosensory (SI) cortex (~BA 3b). Source locations were mapped to the closest points on the cortical surfaces reconstructed from each subject's magnetic resonance imaging scan, morphed to the average brain surface, and visualized using the inflated cortical representation. The inflated representations are used to reveal activity within sulci (dark gray) as well as on gyri (light gray). **B.** Average SI dipole time courses for EA (red) and SA (blue) demonstrate that activity peaks earlier in EA than SA, possibly due to temporal dispersion of afferent signals. Furthermore, SI ECD strength differs between conditions at long latencies, possibly due to the number and/or type of somatosensory fibers recruited. **C.** The image shows distributed source modeling results averaged across subjects and displayed on an average brain surface. These data confirm that the primary sources of magnetoencephalography (MEG) activity are within the contralateral central sulcus. The first significant peak for EA (~20 ms) occurs earlier than that for SA (~35–40 ms) and is located in a slightly more inferior position along the posterior bank of the central sulcus. Response peaks are also seen at ~70 ms and ~120 ms within SI cortex for both EA and SA. Activity returns to baseline by ~250 ms. Thresholds for the activity shown were selected to control the familywise error rate to be at 5%.

result is linearly proportional to the magnitude of the estimated sources.[27,30] The source signals for each individual were smoothed on the cortical surface using a heat-kernel iterative smoothing algorithm (sigma = 1, 10 iterations) prior to across subject averaging.[31] Thresholds for activity maps were calculated by sampling the maximum statistic of 10,000 permutations of data points within the average baseline and evoked response for each individual, an adaptation of a previously demonstrated thresholding method.[32] The maximum statistic was calculated across all sources (in space) for each permutation. The threshold was selected to control the familywise error rate (FWER) to be at 5%. The threshold was determined using this method for each condition and time point separately, using nonoverlapping baseline samples for the different time points.

Analysis of potential correlations between subjective sensations and brain response. To assess the possible relation between *de qi* ratings and brain response, we performed a correlation analysis. To do this, the ECD magnitude at the second somatosensory peak (equivalent to M30 or M35) was determined for each subject. In order to provide readily comparable values across subjects, the magnitude of these peaks was "normalized" by dividing the average absolute value of response occurring between 50 and 70 ms poststimulus. This was done for both EA and SA. The correlation between these values and ratings for the MASS Index as well as the most commonly reported sensations (i.e., those that >60% of subjects reported feeling) was then assessed.

Results

SEFs to EA and SA localize to contralateral SI

MEG data were collected from 15 healthy, right-handed[14] subjects. Each subject underwent 15-minute continuous low-frequency (2 Hz) EA and 15 minutes of continuous low-frequency (2 Hz) SA. In order to spatiotemporally map evoked brain responses to EA and SA, both equivalent current dipole (ECD) analysis[33] and anatomically constrained, noise normalized, distributed source modeling were employed.[27] Source localization with ECD analysis (Fig. 2A) demonstrated that the strongest source of cortical response, at all latencies, for both EA and SA lay within contralateral primary somatosensory (SI) cortex (~BA 3b). This was consistent across multiple subjects with EA and SA sources neighboring one another along SI. These findings were further corroborated by distributed source modeling methods as demonstrated by averaged activity for EA and SA (Fig. 2B). Furthermore, in 11 of 15 subjects, SA sources mapped more dorsally along the homunculus than those for EA, possibly due to differences in the underlying afferent pathways. For ECD dipole placements, the mean Euclidean distance of separation between EA and SA sources (mean ± standard deviation) was significant: 10.79 ± 5.7 mm (two-tailed, $t(15) = 7.38$, $p < 0.001$).

Temporal differences in brain response to EA and SA

Averaged SI dipole time courses for EA and SA (Fig. 2B), showed clear differences in the timing of early (<40 ms) peaks. Response to EA first peaked at 20.95 ± 1.6 ms poststimulus and was followed by another peak at 31.7 ± 3.2 ms. The spatiotemporal distribution of these early peaks appeared similar to the M20 and M30 components evoked by median nerve stimulation.[34,35] Similar to the M20, the early (20 ms) EA ECD was oriented anteriorly while the M30 orientation was reversed. The M20 may reflect information propagating from layer 4 to layers 2/3 in cortex[36–38] and the M30 return currents oriented back toward layer 5[36] or possibly a combination of activity within areas 3b and 3a or 1.[39]

No clear peaks were seen at ~20 ms for SA. Instead, the first clear peak occurred 38.8 ± 2.8 ms poststimulus. This peak was similar in orientation but significantly longer in latency than the corresponding M30 seen for EA (paired *t*-test, $t(15) = 8.14$, $p < 0.001$). Furthermore, both EA and SA demonstrated corresponding peaks at ~55 ms, ~70 ms, and ~120 ms all delayed slightly for SA. These peaks are likely to be analogous to those seen during median nerve stimulation. Finally, it should be noted that early ECD responses to EA and SA were slightly larger in magnitude for SA; however, differences were largest between ~80 and 250 ms (paired *t*-test of average value 80–250 ms, $t(15) = 2.18$, $p < 0.045$).

Psychophysical assessment

Analysis of the sensation expectancy questionnaires indicated that subjects most often *expected* to feel tingling sensations (13/16 subjects reported "Yes") during acupuncture. This was followed by expectancy for deep pressure (6 subjects), aching (5 subjects), and sharp pain (5 subjects). Only 4 subjects based their expectations on prior experience with acupuncture, while 3 indicated their expectations were based on media (i.e., books, TV, or magazines) and conversations with friends. Finally, 7 subjects indicated they had no particular source of information guiding their expectations, and 2 indicated that their rating was based on general perceptions of how a needle would feel.

Following MEG recordings, subjects were asked to evaluate the sensations they felt during both EA and SA by rating their intensity (10-point Visual Analogue Scale). The MASS Index was 4.1 ± 2.0 for EA and 3.4 ± 2.1 for SA (Fig. 3A). Although the score was not significantly different between EA and SA, there was a trend for stronger sensation under EA (paired *t*-test, $t(15) = 1.813$, $p < 0.09$).

When considering the percentage of subjects reporting any given sensation (Fig. 3B) pressure, tingling, aching, dull pain, numbness, and spreading were the most commonly felt (in that order). Of these sensations, pressure, numbness, and spreading were more often indicated for SA, although they had a lower mean intensity as indicated above. Some subjects also reported feeling "other" sensations, which included a "tapping" sensation and "tiredness/fatigue."

Evaluation of poststimulus questionnaires regarding expectancy showed that 7 subjects felt that neither acupuncture run matched their initial expectations of what acupuncture would feel like. While 8 subjects reported the EA run as most closely matching their expectations due to greater sensations of tingling, numbness, heaviness, and/or pricking due to needle insertion. One subject reported that the SA run most matched their expectations due to a feeling of pressure.

Correlation analysis of sensory experience and brain responses

In the current study, sensory ratings were assessed for correlation with MEG data. We did not find any significant cor-

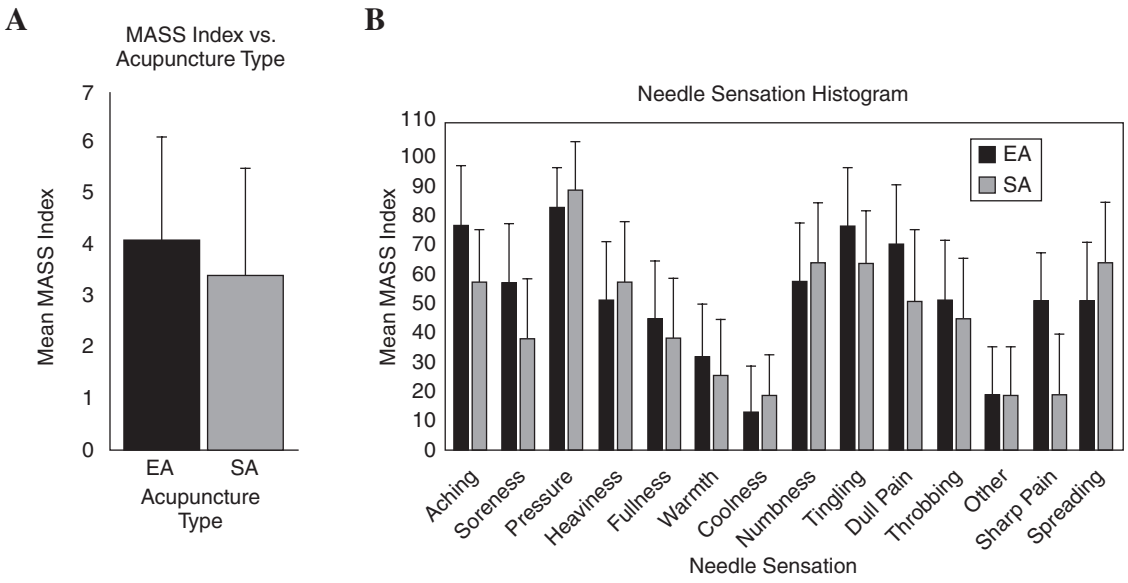

FIG. 3. Post-acupuncture ratings. **A.** The mean MGH Acupuncture Sensation Scale (MASS) Index was on average slightly larger for electroacupuncture (EA) than sham acupuncture (SA), suggesting that in general subjects might have felt stronger sensations during EA. **B.** When considering both EA and SA, the most commonly reported sensations were "pressure" and "tingling," both being reported by >60% of subjects.

relations between subjective sensory experience and the magnitude of early peaks in MEG response.

Discussion

The present investigation spatiotemporally mapped MEG SEFs to 15 minutes of continuous, low-frequency (2 Hz) EA and SA. ECD and distributed source analysis of brain activity demonstrated that during both conditions, the only consistent source of activity across subjects was the contralateral SI cortex. EA and SA sources were located proximal to one another, with those of SA tending to map more dorsally. The spatiotemporal distribution of SEFs to EA demonstrated similarities to those evoked by electrical stimulation of the median nerve; response first peaked at ~21 ms and then ~32 ms poststimulus, mimicking the median nerve M20 and M30 deflections.[34,35] However, the first clear peak for SA appeared slightly later (~38 ms), and long latency responses (>60 ms) were stronger for SA than EA. Evaluation of the somatosensory *de qi* experience with the MASS Index demonstrated that there was a trend toward stronger EA evoked *de qi* than for SA. Collectively, EA and SA evoked clear spatiotemporal differences in brain activity as indicated by MEG SEFs.

Basis of spatiotemporal differences in brain responses to EA and SA

First, there was a general tendency for SA sources to map dorsally to those of EA. One possibility is that deep electrical stimulation (EA) evoked signaling within the median nerve while superficial stimulation during SA primarily recruited afferents carried within the antebrachial cutaneous nerve.[40] The cortical distribution of median nerve afferents, which carry sensory information from the first four digits of the hand, are likely to map inferiorly to those of the antebrachial nerve (carrying signals from superficial, medial forearm receptors) as predicted by the distribution of arm/hand areas along the SI homunculus.[41–46]

Secondly, differences in the timing of early EA and SA responses may be due the nature of these stimuli (i.e., electrical versus mechanical). Specifically, unlike EA, the first clear response to SA peaks at ~38 ms. The lack of a clear ~20-ms peak, as seen with EA, is likely due to temporal dispersion of early SA signals. During electrical stimulation, underlying receptors/afferents are recruited simultaneously; thus, signaling is not spread over time. However, during SA, the mechanical stimulation creates gradual skin indentation (2.5 ms until maximum tip deflection), which may evoke a graded/cumulative recruitment of sensory fibers. Thus, the lack of clear peak at ~20 ms and a slight difference in the slope of response leading to the secondary peak (32 ms for EA and 38 ms for SA) may have resulted from temporal dispersion of afferent sensory signals during SA. Similarly, studies utilizing EEG to investigate differences in brain response to mechanical versus electrical stimuli have found that early components (<30 ms) evoked by mechanical stimulation are often less pronounced and have slightly longer peak latencies[47] than those for electrical stimulation. This has also been noted when comparing SEFs to electrical stimuli with those evoked by airpuffs.[48]

Additionally, SA evoked on average a stronger brain response than EA, particularly at long latencies (>80 ms). This may have resulted from differences in the number and/or type of somatosensory fibers recruited. Although the relatively rapid onset of sensory SEFs (<40 ms) suggests that both EA and SA signals are carried at least in part by fast Aβ sensory fibers, it is possible that the relatively larger surface area of the SA tip excited *more* superficial sensory fibers than EA. Furthermore, EA (because of its electrical and invasive nature) may have more often resulted in concurrent

activation of superficial and/or deep pain fibers, thus decreasing the dynamic range between a qualitatively "strong but not painful" and a painful stimulus. Differences in the magnitude of brain response to acupuncture versus noninvasive control stimulation have also been noted in fMRI studies and attributed to possible differences in signaling pathways.[18,49]

Analysis of the *de qi* experience during acupuncture was determined using the MASS index. Subjects tended to report stronger *de qi* for EA than for SA. To assess the possible relation between differences in intensity ratings for different sensations and individual brain responses, we performed a correlation analysis. However, no significant correlation was found. Furthermore, the similarity of *de qi* sensations experienced were similar for both SA and EA regardless of which sensations subjects expected to feel (as reported in pre-scan questionnaires). Similarly, previous acupuncture research has demonstrated that expectancy does not significantly bias which sensations subjects will actually experience during acupuncture.[50]

Potential relevance of differences in brain responses to EA and SA

Although the present study does not test the clinical efficacy of EA and SA, previous clinical data demonstrate that acupuncture might have therapeutic effects on chronic pain.[51,52] Recent fMRI studies propose that acupuncture efficacy in carpal tunnel syndrome (CTS) is supported by the somatosensory stimulation provided during acupuncture treatment.[53] More specifically, aberrant sensory signaling resulting from nerve entrapment in CTS may cause maladaptive plasticity within SI cortex, symptoms of pain and allodynia, and SI hyperactivity demonstrated by stronger fMRI signals. One possibility is that the somatosensory signals arising from acupuncture stimulation counteract these effects by providing a more constant sensory input to promote normal/healthy plasticity.[53]

The present study demonstrates that brain SEFs to EA and SA strongly involve SI cortex. Potential differences in efficacy between these modalities may be linked to their respective temporal dynamics and how they may influence mechanisms of neuronal plasticity. For example, early SEFs to EA demonstrate temporally succinct activity (peaks); thus, it is possible that EA provides a more temporally synchronous firing of sensory cells leading to more efficient Hebbian-type plasticity. It is also possible that EA may be more effective than SA because it evokes response within deep as well as superficial receptors, which may all be affected in chronic pain syndromes. However, there are no clinical electrophysiologic data to support this assumption. Furthermore, there is no consensus on what form of sham acupuncture is most appropriate and thus other forms may be more or less similar to verum acupuncture, leading to variable clinical response.

Interpreting SEFs in the context of acupuncture fMRI data

In order to elucidate brain processing of acupuncture stimuli, researchers have also utilized fMRI. Data from these studies demonstrate that acupuncture stimulation elicits response within multiple cortical, subcortical, limbic, and brainstem areas.[1,18,49,54–58] Although it may appear that the present data demonstrating localization of evoked MEG brain response to SI cortex conflict with previous fMRI findings of distributed brain response to acupuncture, it is important to acknowledge differences in imaging modality and experimental design/analysis that may affect which brain areas appear to be active during acupuncture. For instance, differences may have resulted both from the short interstimulus interval employed,[34,36] as well as the fact that fMRI and MEG observe different aspects of brain "activity."[1] Furthermore, to evaluate potential MEG activity outside of SI at the present stimulation frequency, different analysis approaches may also be needed. Indeed, our preliminary data assessing oscillatory (rhythmic) brain activity in different frequency bands suggest that during EA there is a strong decrease in induced μ rhythms (8–30 Hz) from ~50 to 350 ms poststimulus within the contralateral SI, bilateral SII, parieto-occipital regions, and in some cases frontal areas[59,60] all overlapping with cortical areas implicated in acupuncture fMRI studies.

Conclusions

The present data offer insights into spatiotemporal differences in brain response to EA and SA. Both EA and SA evoked brain responses that were located within the contralateral primary somatosensory (SI) cortex. However, initial responses for EA peaked slightly earlier than those for SA and were located inferiorly within SI. The average equivalent current dipole (ECD) strength was stronger (particularly at latencies >100 ms) for SA. These spatiotemporal differences between EA and SA are likely attributable to stimulus modality (electrical versus mechanical) and differences in the underlying somatosensory fibers transmitting these signals.

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