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, fifteen healthy subjects were evaluated with magnetoencephalography (MEG) to map the location and timing of brain activity during low frequency electroacupuncture (EA) and, mechanical, non-insertive, 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 (ECD) strength was stronger (particularly at latencies >60ms) for SA. These spatiotemporal differences between activations elicited by EA and SA are likely attributable to stimulus modality (electrical vs. 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 which suggest that acupuncture's therapeutic effects 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.

Keywords

acupuncture; magnetoencephalography; MEG; EEG; MRI; fMRI; somatosensory; SEP; SEF; SI; SII; prefrontal; limbic; pain; alternative; complimentary; medicine; imaging; non-invasive; non-pharmacological

INTRODUCTION

Neuroimaging techniques such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) allow us to non-invasively 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 [for a review see ¹]. However, fMRI only measures hemodynamic changes which 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 non-painful and painful stimuli.

EEG studies investigating the effects of MA on non-painful 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. Yet, similar studies did not find early modulation with arm/hand or facial acupoint stimulation. 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. 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. However, modulation of pain SEPs may occur even when subjects are unconscious under anesthesia and although confounding effects may occur when acupuncture is combined with some anesthetics other data found no effect of acupuncture on pain regardless of whether anesthesia is given prior to or following EA but again the results varied. Finally, the time-courses of EA SEPs and their effects on both non-painful and painful sensory stimuli has been found to be highly dependent on the inter-stimulus interval (ISI) used, with short intervals (<2 seconds), commonly used in clinical settings, resulting in an overlap of long-latency components thus making it difficult to interpret many of these studies.

Collectively, studies of acupuncture effects on non-painful and painful SEPs has produced mixed results and are confounded by the need to use long (≥2 second, which is uncommon for clinical EA) inter-stimulus 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, demonstrates that their concurrent use provides little additional information regarding acupuncture’s neural mechanisms. 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 (2Hz) 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 was collected for 15 healthy, right handed adults, 20-54 years of age (mean 28 ± 9yrs). Subjects were recruited via fliers/newsletters adhering to 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 Massachusetts General Hospital.

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1Somatosensory EEG and MEG studies often utilize paradigms in which sensory stimuli are given repeatedly. Trials are averaged so that evoked brain responses which 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).
The experiment consisted of 5 runs (3 rest runs and 2 acupuncture runs, see Figure 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 are 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 vs. after stimulation. The order of EA and SA runs was randomized across subjects. Both EA and SA consisted of 15 minutes continuous low-frequency (2Hz) 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 towards superficial brain activity, 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 (Figure 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 *deqi* 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: 0.2ms at 2Hz) 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, non-insertive 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 5ms).

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 Q-tips during both runs. Importantly, in order to most closely match active stimulation in the EA run, the SA procedure was two-fold:

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 2Hz mechanical pecking to mimic EA frequency. Stimulation was set to a level at which subjects indicated feeling a “strong” (not painful) sensation. A tactile SA control was chosen over non-invasive electrical stimulation for multiple reasons. First, we felt that surface electrical stimulation would not qualify as sham but instead approximate TEAS acupuncture. Secondly, 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 non-invasive 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 which 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, consisted of a list of thirteen 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 (VAS), 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 *deqi* (i.e. aching, soreness, pressure, heaviness, fullness, warmth, cool, numbness, tingling, and 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 *deqi* 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:

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

where \(S_1\) is the highest intensity score for any *deqi* 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 was also compared between different groups with a Chi-squared 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 you 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 FastTrak digitizer to allow for accurate alignment of the MEG sensor array with the subjects MRI scan. The acquisition bandwidth was 0-400 Hz with a 1200 Hz digitization rate. The subject’s electrocardiogram (ECG) and electro-occulogram (EOG) were recorded simultaneously to control and if necessary remove influence from physiological noise sources such as heart beat, eye blinks and eye saccading.

**High-Resolution, Structural MRI Data Collection:** Individual MRI scans are necessary to assure accurate localization of MEG signals. Each subject underwent an MRI scan which 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 1.5T MRI (Siemens Medical, Erlangen, Germany). Two high-resolution MPRAGE (256x256 matrix (256mm FOV), 128 slices, 1.33mm slice thickness, TE=3.39ms, TR=2530ms, TI=1100ms, flip=7deg) images (averaged offline) and a multi-echo 3D-FLASH scan (256x256 matrix (256mm FOV), 128 slices, 1.33mm slice thickness, TE=5.91, TR=20ms, 3 echos, echo spacing=100 μs, flip=5deg) 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 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 MRI’s [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 ECD’s 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 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 (MNE) [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 inter-subject 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 timecourses 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 PET data, but with a temporal resolution of 5ms 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 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 10000 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 family wise error rate (FWER) to be at 5%. The threshold was determined using this method for each condition and time point separately, using non-overlapping baseline samples for the different time points.

Analysis of Potential Correlations between Subjective Sensations and Brain Response—To assess the possible relation between deqi 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 50-70ms post-stimulus. 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 which >60% of subjects reported feeling) was then assessed.

RESULTS
SEF’s to EA and SA localize to contralateral SI

MEG data were collected from 15 healthy, right-handed [14] subjects. Each subject underwent 15 min 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 was employed [27]. Source localization with ECD analysis (Figure 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 (Figure 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 ± stdev) was significant 10.79 ± 5.7 mm (2-tailed, t(15) = 7.38 p<.001).
**Temporal Differences in Brain Response to EA and SA**

Averaged SI dipole time-courses for EA and SA (Figure 2D), showed clear differences in the timing of early (< 40ms) peaks. Response to EA first peaked at 20.95 ±1.6 ms post-stimulus 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 (20ms) 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 towards layer 5 [36] or possibly a combination of activity within areas 3b and 3a or 1 [39].

No clear peaks were seen at ~20ms for SA. Instead the first clear peak occurred 38.8 ± 2.8 ms post-stimulus. This peak was similar in orientation but significantly longer in latency than the corresponding M30 seen for EA (paired t-test, \( t(15) = 8.14, p<.001 \)). Furthermore, both EA and SA demonstrated corresponding peaks at ~55ms, ~70ms and ~120ms 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 ~80-250ms (paired t-test of average value 80-250ms, \( t(15) = 2.18, p<0.045 \)).

**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 four subjects based their expectations on prior experience with acupuncture while three indicated their expectations were based on media (i.e. books, TV, or magazines) and conversations with friends. Finally, seven subjects indicated they had no particular source of information guiding their expectations and two 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 (10pt VAS). The MASS-Index was 4.1 ± 2.0 for EA and 3.4 ± 2.1 for SA (Figure 3A). Although the score was on 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 (Figure 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 had a lower mean intensity as indicated above. Some subjects also reported feeling “other” sensations which included a “tapping” sensation, “tiredness/fatigue”.

Evaluation of post-stimulus 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 either 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 correlations 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 (2Hz) 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 \( \sim 21 \) ms and then \( \sim 32 \) ms post-stimulus mimicking the median nerve M20 and M30 deflections \([34, 35]\). However, the first clear peak for SA appeared slightly later (\( \sim 38 \) ms) and long latency responses (> 60ms) were stronger for SA than EA. Evaluation of the somatosensory \textit{deqi} experience with the MASS Index demonstrated that there was a trend toward stronger EA evoked \textit{deqi} 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 vs. mechanical. Specifically, unlike EA, the first clear response to SA peaks at \( \sim 38 \) ms. The lack of a clear \( \sim 20 \) ms peak, as seen with EA, is likely due to temporal dispersion of early SA signals. During electrical stimulation, underlying receptors/aferents 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 \( \sim 20 \) ms and a slight difference in the slope of response leading to the secondary peak (32ms for EA and 38ms 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 vs. electrical stimuli have found that early components (< 30ms) 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 SEF’s to electrical stimuli with those evoked by airpuffs \([48]\).

Additionally, SA evoked on average a stronger brain response than EA, particularly at long latencies (> 80ms). 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 vs. non-invasive control stimulation have also been noted in fMRI studies and attributed to possible differences in signaling pathways \([18, 49]\).

Analysis of the \textit{deqi} experience during acupuncture was determined using the MASS index. Subjects tended to report stronger \textit{deqi} for EA than 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 deqi sensations experienced were similar for both SA and EA regardless of which sensations subjects expected to be 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 may 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 as it evokes response within deep as well as superficial receptors which may all be affected in chronic pain syndromes. However, there are no clinical electrophysiological 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 [for review see1, 18, 49, 54-58]. Although, it may appear that the present data demonstrating localization of evoked MEG brain response to SI cortex conflicts 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 inter-stimulus interval employed [34, 36] as well as the fact that fMRI and MEG observe different aspects of brain “activity” [for a brief review see 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 suggests that during EA there is a strong decrease in induced mu rhythms (8-30Hz) from ~50-350 ms post-stimulus 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.

**CONCLUSION**

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 > 100ms) for SA. These spatiotemporal differences between EA and SA are likely attributable to stimulus modality (electrical vs. mechanical) and differences in the underlying somatosensory fibers transmitting these signals.

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References


FIGURE 1. Experimental Design and the Arm Brace

(A) Each MEG scan consisted of 3 rest runs and 2 acupuncture runs (EA and SA). Acupuncture run order was randomized across subjects and consisted of 15 minutes continuous low frequency (2Hz) 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.
Figure 2. ECD and Distributed Source Analysis of EA and SA Conditions

(A) ECD localization for 15 subjects demonstrated that sources for both EA (red) and SA (blue) map proximal to one another along the contralateral SI cortex (~BA 3b). Source locations were mapped to the closest points on the cortical surfaces reconstructed from each subject's MRI, 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

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number and/or type of somatosensory fibers recruited. (C) The image shows distributed source modelling results averaged across subjects and displayed on an average brain surface. These data confirm that the primary sources of MEG activity are within the contralateral central sulcus. The first significant peak for EA (∼20ms) occurs earlier than that for SA (∼35-40ms) and is located in a slightly more inferior position along the posterior bank of the central sulcus. Response peaks are also seen at ∼70ms and ∼120ms within SI cortex for both EA and SA. Activity returns to baseline by ∼250ms. Thresholds for the activity shown were selected to control the family wise error rate (FWER) to be at 5%.
Figure 3. Post-Acupuncture Ratings
(A) The mean MASS-Index was on average slightly larger for EA than SA suggesting that in general subjects may 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.