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The effect of acupuncture on motor cortex excitability and plasticity

Yew Long Lo*, S.L. Cui, S. Fook-Chong

National Neuroscience Institute, Singapore General Hospital, Department of NeurologyOutram Road, Singapore 169608, Singapore

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Abstract

Acupuncture has been used extensively in facilitating motor recovery after stroke. Its mechanism of action remains uncertain. In this sham-controlled study, we demonstrate for the first time that acupuncture has a real and enduring effect on motor cortex functional changes, in terms of cortical excitability and output mapping using transcranial magnetic stimulation.

Keywords: Acupuncture; Transcranial magnetic stimulation; Cortical excitability; Motor cortex; Plasticity

Acupuncture is a therapeutic technique increasingly employed in the treatment of neurological disorders [15]. However, its mechanism of action remains uncertain. Although extensively studied, conflicting data have emerged regarding its efficacy in facilitating motor recovery after stroke [25,13].

We have previously used transcranial magnetic stimulation (TMS) to demonstrate changes in motor cortex excitability with acupuncture. Right cortex TMS showed reduced cortical excitability, and a tendency to an increase in cortical excitability was observed with left cortex TMS [18]. It is well recognized that sensory input can produce persistent changes in the organization of the motor cortex [14,11], which may be beneficial in neuro-rehabilitation [1]. We hypothesized that acupuncture may represent a form of somatosensory input capable of modulating motor cortex changes [17].

With ethics committee approval, eight healthy subjects (four men) aged 21 to 50 with no previous experience in acupuncture were studied, with informed consent. Subjects were seated comfortably in a quiet environment. TMS was delivered to the left motor cortex using a Magstim 8-shaped coil (Magstim, Whitland, UK) 70 mm in diameter generating a peak magnetic field of 2.2 T, in conjunction with a Magstim 200 unit. MEPs were elicited with stimulation intensity at 10% above the relaxed threshold [22] using right first dorsal interosseous (FDI) recordings. Throughout the study, only left TMS and right FDI recordings were made. Ten consecutive baseline MEPs, recorded with surface adhesive electrodes (Medtronic 9013S0241; Medtronic, Skovlunde, Denmark) using the belly-tendon configuration, were obtained before (baseline) each acupuncture or sham procedure at 10-s intervals. During TMS, subjects were advised to stay alert but relaxed. Continuous EMG and sound monitoring ensured only non-facilitated responses were included for analysis. MEP responses were amplified, filtered and recorded on a Dantec Counterpoint electromyography machine (Dantec, Skovlunde, Denmark) with a band pass of 20 to 2000 Hz for analysis.

Acupuncture needling was performed by an experienced acupuncturist under aseptic conditions using disposable Hwato acupuncture needles (Suzhou Medical Appliance Factory, Suzhou, People's Republic of China) measuring 0.25 mm in diameter and 25 mm in length. The 'lifting and thrusting technique' was employed without needle rotation, with depth of insertion approximately 1.5 cm. The 'Shousanli' (Large intestine or LI 10) point was chosen in view of its reported effects on the motor system [4]. This was defined approximately as 1/6 of the distance below the elbow, along a line joining the anatomical snuffbox base and the lateral end of the elbow crease. It was not within the ulnar innervation of the FDI, to avoid possible afferent effects from direct sensory nerve needling. An ipsilateral sham point not corresponding to any known acupoint was chosen as a control. This was located on the ipsilateral forearm, 2 cm medial to the above

* Tel.: +65 63265003; fax: +65 62203321.
E-mail address: gnrlyl@sgh.com.sg (Y.L. Lo).

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acupoint, at the same level below the elbow. An identical needle of similar depth was inserted. Mean peak-to-peak MEP amplitudes (in mV) and onset latencies (in ms) were compared statistically using repeated-measure ANOVA), with a *p* value below 0.05 considered as statistically significant.

'H' reflex measurements from the ipsilateral flexor carpi ulnaris (10 stimulations for each acupoint or sham needling condition) instead of TMS were additionally obtained in five subjects using the same acupuncture procedure. Each subject completed three sessions with acupoint needling (5, 10 and 15 min with needle in situ) and three sessions with sham needling in a randomized order. During each session, 10 baseline MEPs were obtained, followed by acupuncture or sham needling of respective durations. Another 10 stimuli were delivered again before needle removal, and then at 5, 10 and 15 min after needle removal. Each session was separated by a 2-day interval to ensure there were no leftover effects from the previous session. In addition, the acupuncture and sham acupuncture sessions were performed in a randomized fashion.

Motor output mapping was performed in three separate subjects with the magnetic coil positioned tangential to the scalp for inducing an antero-medial current at 45° to the saggital plane. A tight fitting cap comprising 70 grid positions 1 cm apart antero-posteriorly and medio-laterally was placed on the scalp, with the 'hot spot' (point eliciting MEPs of lowest threshold and highest amplitude) in the center of the grid. Each position was stimulated five times at 110% threshold at 5-s intervals. A position was considered unexcitable if all five stimuli failed to elicit an MEP at an oscilloscope gain of 50 uV/division. While obtaining output maps, the number of excitable positions, mean MEP amplitude and center of gravity (COG) at each position were recorded. The COGs were calculated with the formula $[\sum_i a_i x_i / \sum a_i,\ \sum_i a_i y_i / \sum a_i]$ for scalp sites (x_i, y_i) in cm from the vertex and a_i as amplitude in mV. As the 10-min acupoint needling resulted in significant facilitation of MEP amplitudes, mapping was performed with this condition after baseline output maps were completed and again at 15 min after needle removal, in order to minimize the number of stimuli given per subject. Additionally, mapping was also carried out with the 10-min sham needling condition.

A two-factor repeated-measure ANOVA was first performed to compare MEP amplitudes over the five time points (baseline, with needle in situ, 5, 10 and 15 min after needle removal), with needling duration (3 levels: 5, 10, and 15 min) and needling condition (2 levels: acupoint or sham needling) as factors. This showed that both needling duration ($p < 0.0005$) and needling condition ($p = 0.022$) were significant. Furthermore, there was significant interaction between these two factors ($p = 0.009$), implying a real effect of needling with needling condition on MEP amplitude.

We followed with post hoc analysis (Student–Newman–Keuls), which showed that acupoint needling resulted in significantly facilitated MEP amplitudes compared with baseline for the 10 and 15 min needling duration. These effects were evident 5 min after needle removal, up to a maximum of 15 min ($p = 0.001$, 0.023 and <0.0005, respectively for 10 min needling; $p = 0.03$, 0.005, and 0.006, respectively for 15 min needling). The 5-min duration resulted in depression of MEP amplitudes seen only at 5 min with the needle in situ ($p = 0.035$).

Using sham needling, significant depression of MEP amplitudes was evident with the 5 and 10 min needling durations, only at 5 and 10 min after needle insertion, with the needle in situ ($p < 0.005$ and $p = 0.049$, respectively). The rest of the experiment, whereby the needle was removed, did not result in significant MEP amplitude changes (Fig. 1). There were no significant effects of acupoint or sham needling on MEP latency.

Similarly, 'H' reflex amplitudes and H amplitude/M amplitude ratios were not significantly affected using similar statistical calculation methods.

Mean relaxed motor threshold of 73.2% (standard deviation (S.D.): 10.1) (average for each session of acupoint needling) and 72.2% (SD: 6.5) (average for each session of sham needling) were also not significantly different (unpaired Student's *t*-test, $p = 0.77$).

Motor output mapping with acupoint needling in three separate subjects demonstrated significant increases in the number of excitable positions (unpaired Student's *t*-test, $p < 0.05$). Actual excitable positions increased from 3 to 7, 4 to 13 and 3 to 7, respectively. Using sham needling in three other subjects, however, the number of excitable positions remained unchanged in two subjects (5 to 5, 7 to 7) and slightly reduced from 8 to 6 in one subject (unpaired Student's *t*-test, $p = 0.56$). Mean MEP amplitudes above 0.5 mV significantly increased from baseline with acupoint needling (0.56–1.11 mV) (unpaired Student's *t*-test, $p < 0.01$) but this was not seen with sham needling (0.67–0.62 mV, unpaired Student's *t*-test, $p = 0.2$). Mean center of gravity (COG) coordinates with acupoint shifted anteriorly, from (3.68, 1.6) to (3.9, 5.77). This was statistically significant for the *y* coordinate (Student's *t*-test, $p < 0.05$). With sham needling the mean COG shifted from (3.85, 3.33) to (3.12, 2.63). Both *x* and *y* coordinate changes were not significant ($p = 0.55$ and 0.41, respectively) (Fig. 2).

The present study demonstrated that acupuncture, even with removal of the needling stimulus, led to enduring changes in cortical excitability and plasticity. Significant increases in motor map sizes, COG, absence of latency changes and lack of modulatory effect on the 'H' reflex was evidence supporting the presence of a supraspinal mechanism. There were also no significant motor threshold differences from which stimulating intensities were based between the acupuncture and sham conditions. Furthermore, the findings of significant motor map changes with acupuncture in contrast to sham needling for three separate subjects revalidated the original results.

Several pertinent aspects of the findings are emphasized. Firstly, our results show that a novel stimulus was capable of inducing functional motor cortex changes for the first time.

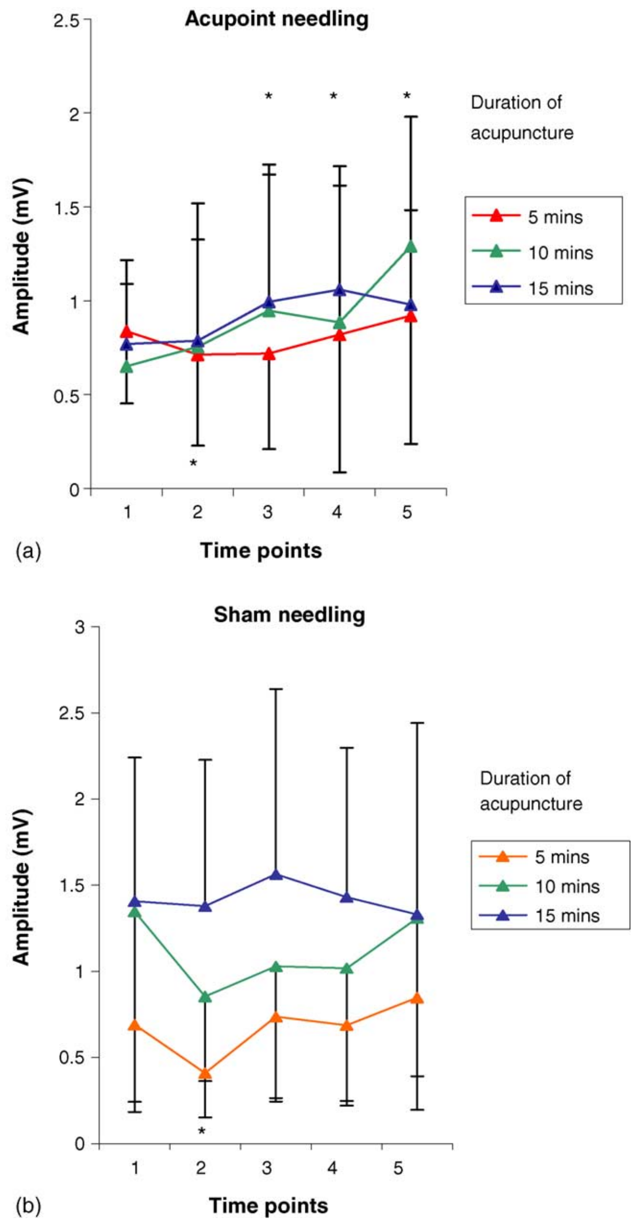

Fig. 1. Graphical illustration of mean MEP amplitudes over the five time points for acupoint and sham needling conditions. The time points refer to baseline, with needle in situ, 5, 10 and 15 min after needle removal, respectively. Error bars depict 1 standard deviation from the mean. Asterisks indicate statistical significance compared with baseline. The levels of significance are as indicated in text.

Second, the findings, contrasted with those from the previous study [18], show that different acupoint needling may lead to differential modulation of cortical excitability, although slight inherent differences in experimental protocols exist. Thirdly, significant changes in cortical plasticity depend on the duration of acupuncture, and were seen only with acupoint needling of at least 10-min duration. In fact, 5 min of acupuncture resulted in a transient effect of MEP amplitude depression when the needle was in situ. This was also seen with sham needling of 5 and 10-min duration, again only with the needle in situ. The 15-min sham needling condition did not result in any significant MEP amplitude change. These findings can be explained in relation to the inhibition of motor cortex excitability by painful cutaneous and muscle stimuli [16,5]. Finally, the demonstration of distinctive effects of acupuncture and sham needling suggests the participation of different neural mechanisms, and that acupoint needling had a real effect in modulating cortical plasticity changes which not attributable to non-specific arousal effects.

In summary, the onset of acupuncture effect depends on a minimum duration of needle insertion. Failure in achieving this may result in the activation of a separate mechanism amounting to opposite effects. The acupuncture effect has a rapid onset (5 min after needle removal) and lasts at least 15 min after needle removal, according to our experimental protocol.

What are the candidate mechanisms responsible for our findings? Somatosensory input in the form of peripheral nerve stimulation [21], limb amputation [23] and ischemic nerve block [2] all result in changes in motor cortex excitability. Motor cortex plasticity changes from electrical stimulation have also been shown to be of functional relevance in promoting improvement of swallowing function for stroke patients [9,19].

Afferent impulses induced by acupuncture have been shown to be mainly transmitted by Aβ and Aδ fibers [10,12]. Hence, acupoint needling, with the resultant 'acupuncture sensation', is likely to be propagated likewise. The afferent ascending volleys may then contribute to driving plastic changes in the motor cortex. Studies relating to anatomical localization of acupoints have identified muscle spindles and other mechanoreceptors [28] at these sites, which are also well documented to influence cortical excitability in human studies [24].

Few functional MRI studies published to date have demonstrated acupoint motor cortex activation, in contrast to non-acupoint stimulation in human [7] and animals [6]. Although the evidence corroborated ours in terms of spatial localization, enduring effects in motor cortex functional modulation, to our knowledge, has not been documented. In this respect, our observations have extended evidence from imaging and validated the presence of enduring motor cortex plastic changes using TMS electrophysiologically.

Much of the published data relating to neurotransmission mechanisms were from electroacupuncture [27]. Bursts of electrical stimuli at specific frequencies have been shown to facilitate the release of neuropeptides, which mediate its pain relieving effect [20]. Our findings, which pertain to motor cortex plasticity with manual acupuncture, have not been addressed to date in terms of neurotransmitter release mechanisms.

The rapid onset of motor cortex plasticity favors changes in synaptic efficacy [8] over intracortical network structural modification [26] as a mechanism in play. Short-term potentiation (STP) and long-term potentiation (LTP) are possible underlying processes. This form of STP or LTP may be a

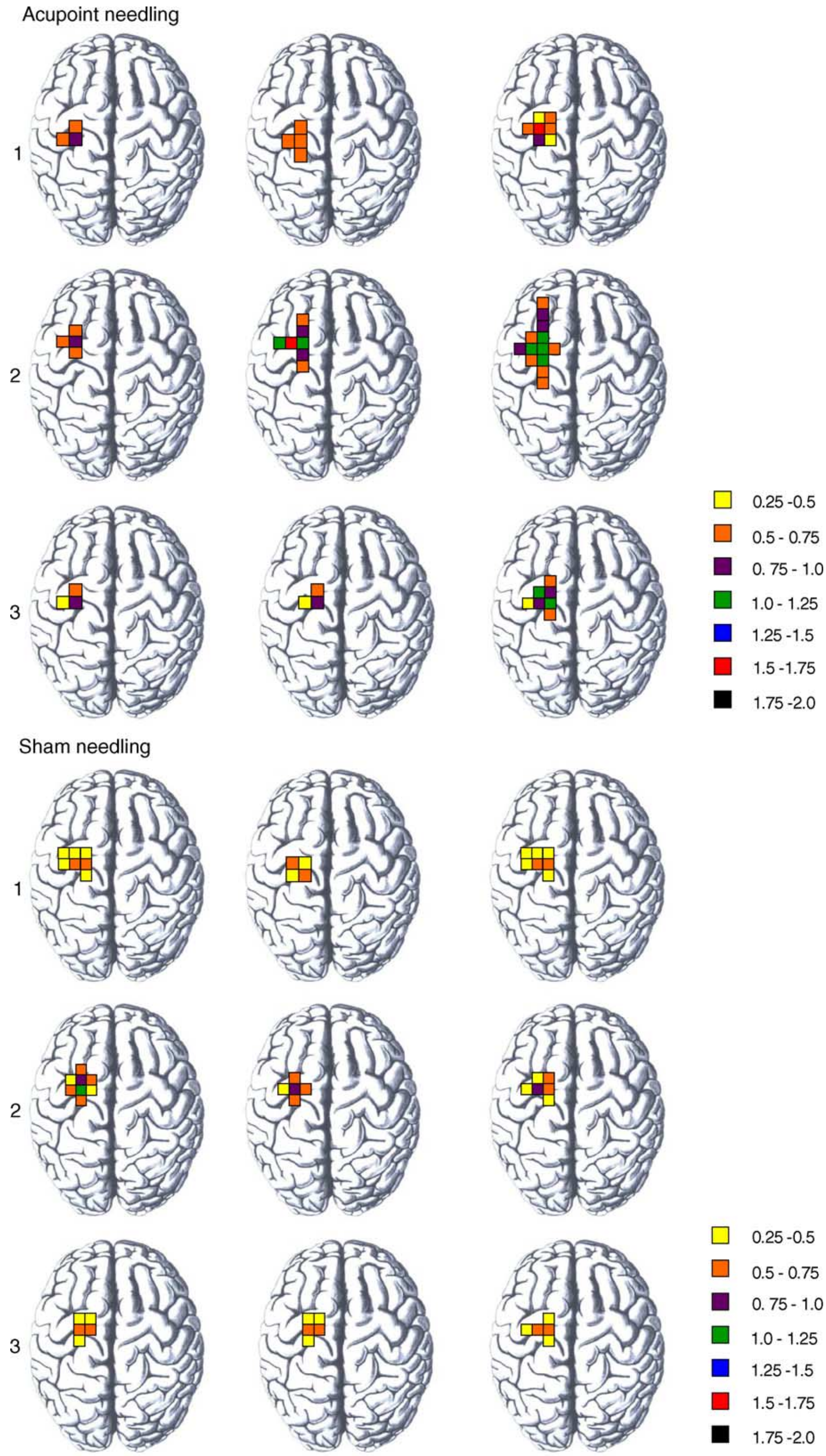

Fig. 2. Motor output maps in three separate subjects for acupoint and sham needling conditions. For each subject, baseline, needle in situ (10 min needling condition) and 15 min after needle removal. Significant output map changes were evident only with acupoint needling. MEP amplitudes were in mV.

possible mechanism of synaptic plasticity, which explain our findings [3].

It should be emphasized that this study showed changes in a controlled experimental setting, and actual functional relevance needs to be further investigated. Our demonstration of functional motor cortex changes driven by this novel input may provide the motivation for future well-designed, randomized clinical trials relating to motor rehabilitation using acupuncture or electroacupuncture.

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