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The role of visual expectations in acupuncture analgesia: A quantitative electroencephalography study

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Abstract

Acupuncture is a complex treatment comprising multisensory stimulation, including visual and tactile sensations and experiences of body ownership. The purpose of this study was to investigate the role of these three components of acupuncture stimulation in acupuncture analgesia. 40 healthy volunteers participated in the study and received acupuncture treatment under three different conditions (real-hand, rubber-hand synchronous, and rubber-hand asynchronous). The tolerance for heat pain stimuli was measured before and after treatment. Brain oscillation changes were also measured using electroencephalography (EEG). The pain tolerance was significantly increased after acupuncture treatment under all three conditions. Noticeable *deqi* (needle) sensations in response to acupuncture stimulation of the rubber hand were found under both rubber-hand synchronous and rubber-hand asynchronous conditions. *Deqi* sensations were significantly correlated with acupuncture analgesia only under the rubber-hand synchronous condition. Increased delta and decreased theta, alpha, beta, and gamma waves were observed after acupuncture treatment under all three conditions. Our findings clarified the role of cognitive components of acupuncture treatment in acupuncture analgesia through the rubber-hand illusion. This study is a first step toward separating various components of acupuncture analgesia, i.e. visual, tactile, and body ownership, and utilizing those components to maximize analgesic effects.

Keywords

Acupuncture analgesia, body ownership, *deqi* sensation, electroencephalography, rubber-hand illusion

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Introduction

Acupuncture is a complex treatment comprising multisensory stimulation that interacts with various factors.[1] Not only tactile but also visual components of acupuncture stimulation are involved in acupuncture analgesia. Recently, phantom acupuncture, which lacks the somatosensory component of acupuncture treatment, was developed by playing video clips of acupuncture treatment.[2–4] Such phantom acupuncture can induce autonomic responses similar to acupuncture in healthy volunteers[3] and pain relief among patients with low back pain by shifting attention to the self and disengaging physical pain processing.[2,4] Furthermore, pain can be modulated by watching a video of acupuncture administered to one's own body.[5,6] Video-guided acupuncture imagery might be beneficial for short-term pain severity reduction in patients with chronic low back pain,[5] although more definitive evidence is needed. Furthermore, an imagined experience of acupuncture increased the pain threshold through deactivation of the

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rostral anterior cingulate cortex and regional connectivity and structural changes in the anterior insula.[6,7] These studies highlight the importance of credibility in the acupuncture treatment context.

Body ownership, the feeling that one's body belongs to oneself, is regarded as a crucial factor in self-awareness.[8] The rubber-hand illusion (RHI) is a multisensory integration paradigm that is used experimentally to manipulate body ownership of the hand,[9] usually by congruent associations of tactile and visual information. A few studies have identified the effect of body ownership in the brain-body responses to acupuncture. For example, when modifying bodily awareness by manipulation of bodily ownership and visual expectation using RHI, the visual expectation of needle stimulation exhibited a greater sympathetic activation to acupuncture stimulation.[10] In addition, successful RHI significantly reduced brain activation in the insula during acupuncture stimulation to the real hand.[1] When the rubber hand was fully incorporated with subjects' own bodies, acupuncture stimulation to the rubber hand produced *deqi* sensations as well as brain activations associated with the interoceptive system, such as dorsolateral prefrontal cortex and insula.[11] Lee et al. also demonstrated the neural circuits involved in the recovery of body ownership by visual and tactile component of acupuncture, and they found a crucial role of the connectivity patterns between the parietal and frontal multimodal areas.[12] Recently, placebo treatment applied to a rubber hand during RHI was shown to produce placebo analgesia, indicating that embodiment might influence placebo effects.[13] Furthermore, looking at a virtual body collocated with the real one can have analgesic effects.[14] However, to date no study has investigated the role of multiple components (visual, tactile, and body ownership) which affect acupuncture analgesic effects using RHI paradigm and electroencephalography (EEG).

The aim of this study was to investigate the role of three components of acupuncture stimulation (visual, tactile, and body ownership) in acupuncture analgesia using the RHI paradigm. In this study, we compared the pain reduction capabilities of acupuncture treatment involving (1) a real-hand condition (Real: visual, tactile, and body ownership components), (2) a rubber-hand synchronous condition (Sync: visual and body ownership components), and (3) a rubber-hand asynchronous condition (Async: visual component only). We also examined changes in brain oscillations during acupuncture treatment under the three different conditions using EEG.

Methods

Participants

In total, 40 healthy right-handed participants (19 male and 21 female, age = 22.6 ± 13.2) recruited by advertisement from Kyung Hee University took part in this 3-day experiment. The participants had no history of cardiovascular disease, neurological or psychological disorders, cognitive impairments, or pain disorders; they were also prohibited from consuming alcohol, caffeine, or any other drugs during the experiments. Among them, 30 participants had previously experienced acupuncture treatment while 10 participants had no experience. They were informed about the experiment and told that they could withdraw from the study at any time without penalty or loss of benefits. All participants provided written informed consent. This investigation was conducted in accordance with the guidelines issued by the Human Subjects Committee and approved by the Institutional Review Board (IRB) of Kyung Hee University, Seoul, Republic of Korea (IRB approval number: KHSIRB-20-101). The trial was registered with the Clinical Research Information Service (CRIS, Trial Registration Number: KCT0005584).

The effect size d of analgesic effect between post-treatment and pre-treatment in open-label placebo acupuncture was about 0.43 based on our previous study.[15] Considering the effect size of placebo analgesia in the previous study, we estimated that approximately 40 participants would be needed in each group for alpha level 0.05 and 80% power.

Experimental design and procedures

The setup of the RHI experiments followed standard procedures and was executed almost identically to the previous studies, i.e. by placing a rubber hand in front of participants while their left hand was hidden from sight. The experiments employed a within-subject cross-over design with three conditions: (1) a real-hand condition (Real: visual, tactile, and body ownership components); (2) a rubber-hand synchronous condition (Sync: visual and body ownership components); and (3) a rubber-hand asynchronous condition (Async: visual component). The experiment included four sessions: (1) pre-pain rating and pre-session rest (240 s); (2) brush-stroking session (150 s); (3) needle stimulation session (600 s: intervals of stimulation ranged from 6–10 s); and (4) post-pain rating and post-session rest (240 s). EEG was recorded throughout the entire experiment and the EEG analysis was conducted during two rest periods before and after treatment. For all three conditions, an acupuncture needle was inserted at acupoint LI4 on the hand before the beginning of the RHI induction session, and participants received 10 min of acupuncture needle stimulation to the left hand (real or rubber hand) immediately after brush stroking (Figure 1(a)).

Participants experienced the three conditions on three separate days. On the first day, the Real condition was used to allow participants to experience both acupuncture and the associated *deqi* sensations. The rubber-hand conditions (Sync and Async) were conducted on the second and third days in random order selected by applying the random function in Excel. Sham acupuncture relies on the visual impression that the needle is being inserted to the skin.[16,17] It has been commonly used as a placebo control for acupuncture

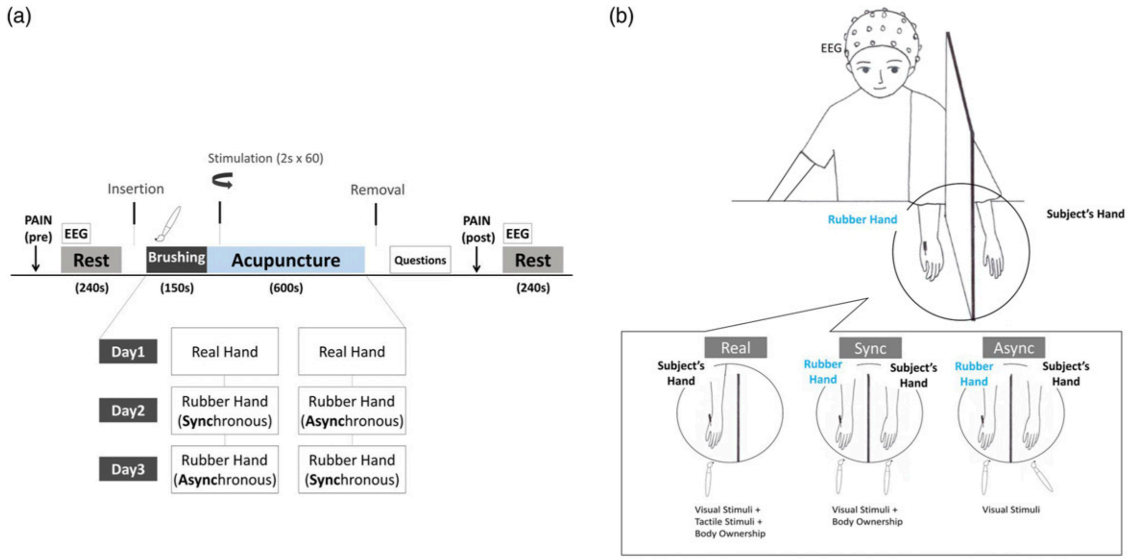

Figure 1. (a) Experimental procedures. The experiment included four sessions: (1) pre-pain rating and pre-session rest (240 s); (2) brush-stroking session (150 s); (3) needle stimulation session (600 s: intervals of stimulation ranged from 6–10 s); and (4) post-pain rating and post-session rest (240 s). (b) Experimental conditions. Two paintbrushes were used to stroke the rubber hand and the participant's own hidden left hand synchronously under one condition (synchronous condition: Sync) and asynchronously under the other condition (asynchronous condition: Async). The acupuncture was applied at acupoint LI4 on the participant's left hand for the Real condition, and the same acupoint on the rubber hand was stimulated for the Sync and Async conditions.

research. However, the validity was limited when using sham acupuncture out of sight of the participants.[18,19] Due to limitations of sham acupuncture, we did not include the fourth condition (sham acupuncture on the real hand) in this study.

Pain measurement

Heat pain stimuli were applied to the right index finger before and after the acupuncture stimulation session. Pain tolerance (finger withdrawal latency) for thermal pain were measured using a heat pain device (Ugo Basile, Italy). This device can measure the nociceptive tolerance accurately using infrared heat stimuli to the finger.[20,21] Participants were told to withdraw their fingers when they could no longer tolerate the pain caused by the heat stimulation. A practice session for heat stimuli before the start of the session involved applying the stimuli to their right middle finger.

To estimate the amount of temperature when subjects were delivered heat stimuli, the temperature was additionally measured using thermosensor (Temperature Pods, ADInstruments, Bella Vista, Australia) (Supplementary Figure 1). In this study, we evaluated the finger withdrawal latency as pain tolerance and the amount of the temperature varied.

Rubber-hand illusion induction

Participants were instructed to fixate on the rubber hand (Korean Prosthetic Limbs Research Institute, Seoul, Korea), not to look elsewhere, and to focus on the sensations of the hand they were viewing. They were also told not to move any of their fingers or their body. The distance between the lateral side of the rubber hand and the participant's own hand was set at 15.5 cm. Different-sized rubber hands were used according to sex (male: 38 cm, female: 32 cm). The acupuncture needle was inserted into the rubber hand at acupoint LI4. Two paintbrushes were used to stroke the rubber hand and the participant's own hidden left hand synchronously under the Sync condition and asynchronously under the Async condition. To maintain the timeline of the experiment, under the Real condition, we also stroked the participant's left hand using the same paintbrush. Participants were told that stroking was used to assess how the brain reacts to tactile stimuli (Figure 1(b)).

After brush stroking for 150 s, acupuncture stimulation to the rubber hand was performed for 10 min. After the acupuncture stimulation sessions were completed, participants rated their perception of RHI using the Rubber Hand Illusion Perception Scale, which includes six questions. The first three questions (Q1–Q3) were the main question and were designed to correspond to the RHI. The last three items (Q4–Q6) were control question. In this study, the questionnaire items were adapted from Mohan[22]'s study consisting of six questions. At the end of the session, participants were also instructed to provide detailed answers in an open-end interview about their experience of RHI induction and changes in their perception during the experiment.

Acupuncture stimulation and *deqi* sensation rating

Acupuncture needle stimulation was applied by a licensed and experienced Doctor of Korean Medicine (D.C.) and consisted of rotating the needle at a frequency of 1 Hz for a period of 2 s: 60 stimulations were included over 10 min of acupuncture stimulation, with intervals between acupuncture stimulations ranging from 6–10 s. Acupuncture needles, 40 mm long and 0.20 mm in diameter, were inserted about 15 mm deep (K.M.S, Chungcheongnam-do, Republic of Korea). Before the experiment, the practitioner was trained for acupuncture manipulations using Acupuncture Manipulation Education System in order to deliver the similar visual expectations on acupuncture stimulation.[23,24]

All participants received acupuncture stimulation at acupoint LI4 on the dorsum of the left hand, radial to the midpoint of the second metacarpal (Real). The LI4 acupoint is widely used for analgesic effects and was simple to use in this experiment due to its position on the hand. Under the rubber-hand conditions (Sync/Async), participants received acupuncture stimulation to the rubber hand with the needle inserted at the same location as for the real-hand condition. After the acupuncture stimulation, participants were asked to rate the intensity of *deqi* sensations (soreness, aching, deep pressure, heaviness, fullness/distension, tingling, numbness, sharp pain, dull pain, warmth, cold, and throbbing) on a scale from 0 (no perceived tactile sensation) to 10 (very intense tactile sensation) using a Korean version of the Massachusetts General Hospital Acupuncture Sensation Scale (MASS), and the sum of sensation values was then calculated.[25]

Electroencephalography recording and analysis

This study used a 32-channel EEG device (BrainAmp Family, BrainProduct, GmbH, Germany) with electrodes placed at 10–20 system channel locations (Fp1, F3, F7, FT9, FC5, FC1, C3, T7, TP9, CP5, CP1, Pz, P3, P7, O1, Oz, O2, P4, P8, TP10, CP6, CP2, Cz, C4, T8, FT10, FC6, FC2, F4, F8, Fp2). The Fz electrode was used as the reference channel, and the ground electrode was located at the forehead. The EEG sampling rate was set to 1000 Hz.

EEG data were preprocessed using Brain Vision Analyzer software (Brain Vision Analyzer, BrainProduct, GmbH, Germany). Raw data were down-sampled to 250 Hz and submitted to a 1–40 Hz band-pass filter. Epochs were removed if the peak signal amplitude exceeded ±200 μV.[26] Frequency analysis was performed using the fast Fourier transformation (FFT) algorithm through a Hamming window. The power spectral density was computed for two epochs each lasting 4 min based on the markers representing the initial time-point: pre-acupuncture treatment and post-acupuncture treatment. The number of artifact was 110.2 ± 152.7 for the Real condition, 52.1 ± 96.1 for Sync condition, 52.1 ± 60.2 for Async condition. No significant differences in number of rejected data were found between conditions ($F = 2.58$, $p > 0.05$). Based on the power spectrum obtained by frequency analysis, the power values for each frequency bandwidth were calculated for delta waves (1–4 Hz), theta waves (4–8 Hz), alpha waves (8–12 Hz), beta waves (12–25 Hz), and gamma waves (25–40 Hz).

The ratio (%) for the power value of each background EEG activity was calculated using a formula similar to that in a previous study[27]: delta ratio (%) = power of delta wave/sum of each power value × 100. The theta ratio (%), alpha ratio (%), beta ratio (%), and gamma ratio (%) were calculated in a similar manner. Because the brain oscillation patterns were similar across electrodes, brain oscillations responses were averaged across electrodes in the present study. Each power ratio was calculated as the power in each band divided by the total spectral power. We used this ratio formula to control variability in the EEG absolute power due to individual differences, such as electrode impedance and scalp thickness.[28]

Statistical analysis

Values are reported as means ± standard deviations. RHI ratings and *deqi* ratings under each condition were compared using paired *t*-tests and one-way analysis of variance (-ANOVA), respectively. Pain tolerance and EEG changes under the Real, Sync, and Async conditions were averaged within the same trials and analyzed using a two-way repeated-measures ANOVA with Tukey's post hoc tests and with time and condition as factors. The significance level was set at 0.05 for all analyses. Statistical analyses were performed using *Jamovi* Software (version 1.2, https://www.jamovi.org). We applied Benjamini-Hochberg method to control the false discovery rate at level alpha. For exploratory data analysis, Pearson's correlation analysis was also performed to determine the correlation between *deqi* sensation and EEG changes, and pain tolerance changes.

Results

Perception of the rubber-hand illusion

The paired *t*-test revealed a significant difference between the Sync and Async rubber-hand conditions in the self-reported perception of the RHI main questions (Sync: 2.04 ± 1.01, Async: −0.76 ± 1.62; $t = 11.9$, $p < 0.001$) (Figure 2).

Perception of *deqi* sensation

The one-way ANOVA revealed significantly greater *deqi* sensations under the Real condition than under the two rubber-hand conditions, and also revealed prominent *deqi* sensations under the rubber-hand conditions (MASS score sums: Real: 26.02 ± 19.42; Sync: 12.27 ± 15.11; Async: 9.48 ± 14.08, $F = 9.906$, $p < 0.001$; Figure 3(a)). Both the Sync and Async rubber hand condition exhibited noticeable

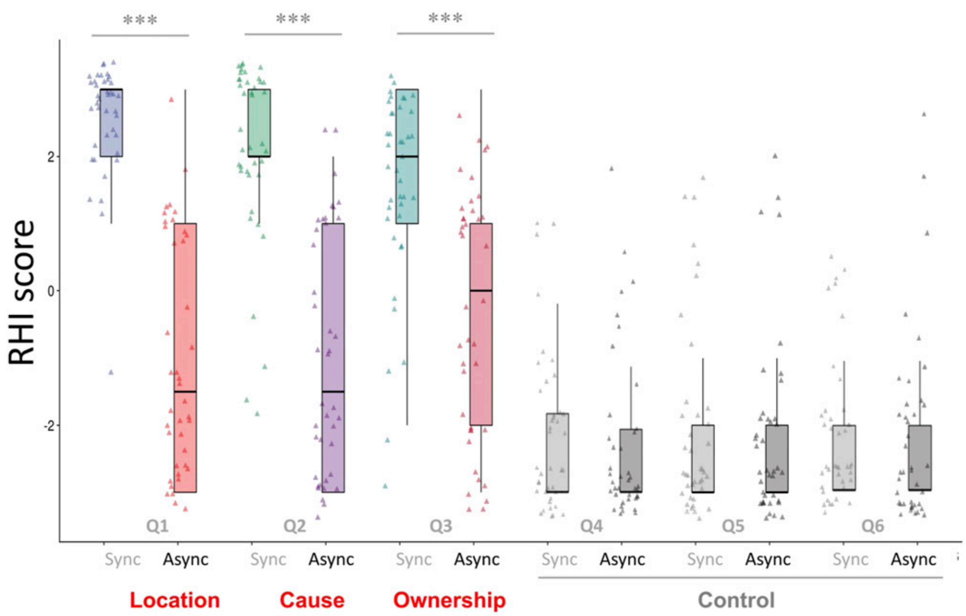

Figure 2. RHI questionnaire and *deqi* sensation ratings under each condition. (a) Comparison of RHI questionnaires between the Sync and the Async conditions. Q1. It seemed as if I were feeling the touch of the paintbrush in the location where I saw the rubber hand touched. Q2. It seemed as though the touch I felt was caused by the paintbrush touching the rubber hand. Q3. I felt as if the rubber hand were my hand. Q4. It felt unpleasant when the brush touched my hand. Q5. My left hand felt cold. Q6. My left foot felt cold. The first three questions (Q1–Q3) were the main question and were designed to correspond to the RHI. The last three items (Q4–Q6) were control questions. Responses to RHI questionnaire items used a 7-point Likert scale ranging from "strongly disagree (−3)" to "strongly agree (+3)." Results are reported as means with standard deviations. A significant difference in responses to the RHI perception scale was observed between the brush-stroke sessions under the Sync and Async rubber-hand conditions.

experiences of the *deqi* sensation (One sample t-test, Sync: $t = 5.13$, $p < 0.001$, Async: $t = 4.26$, $p < 0.001$). However, the paired t-tests showed no significant differences in *deqi* sensations when the Sync and Async rubber-hand conditions were compared. Each MASS questionnaire under three different conditions is represented by heat map (Figure 3(b)).

Changes in pain tolerance

The repeated-measures ANOVA showed a significant effect of time ($F = 51.00$, $p < 0.001$). However, no significant effect was observed for condition ($F = 0.419$, $p = 0.659$) and no time × condition interaction was found ($F = 1.48$, $p = 0.232$) (Figure 4). Results of the paired t-test revealed that the pain tolerance was significantly increased after acupuncture stimulation under the real-hand condition (Real: pre-acupuncture (pre): 8.75 ± 2.40, post-acupuncture (post): 10.67 ± 4.26, $t = -4.04$, $p < 0.001$, Benjamini-Hochberg (B-H) corrected). Similarly, results of the paired t-test indicated that the pain tolerance was significantly increased after acupuncture stimulation under both the Sync and Async conditions (Sync: pre: 9.57 ± 3.52, post: 10.71 ± 4.18, $t = -3.39$, $p < 0.01$, B-H corrected; Async: pre: 9.37 ± 2.86, post: 11.45 ± 4.39, $t = -4.91$, $p < 0.001$, B-H corrected).

There were no significant differences of increased pain tolerance between visit two and visit three in the Sync condition (0.73 ± 1.19 vs 1.53 ± 2.72, $t = 1.200$, $p > 0.05$) and in the Async condition (1.75 ± 3.09 vs 2.44 ± 2.20, $t = 0.859$, $p > 0.05$). There were no significant differences of increased pain tolerance between their visit order (day 2 or day 3) in the Sync and the Async condition.

Changes in electroencephalography power

Increased delta and decreased theta, alpha, beta, and gamma waves were observed after acupuncture treatment under all three conditions (Table 1; Figure 5). For all conditions, the delta wave ratio increased significantly after the acupuncture stimulation. The repeated-measures ANOVA showed a significant effect of time ($F = 220.867$, $p < 0.001$), but no effect of condition ($F = 1.34$, $p = 0.266$) or time × condition interaction was found ($F = 0.181$, $p = 0.835$).

Under all conditions, the theta ratio decreased significantly after the acupuncture stimulation. The repeated-measures ANOVA revealed a significant effect of time ($F = 105.58$, $p < 0.001$), but no effect of condition ($F = 1.12$, $p = 0.330$) or time × condition interaction was found ($F = 1.10$, $p = 0.337$).

For all conditions, the alpha ratio decreased significantly after the acupuncture stimulation. The repeated-measures ANOVA again revealed a significant time effect ($F = 198.7$, $p < 0.001$), but no effect of condition ($F = 0.119$, $p = 0.888$) or time × condition interaction was found ($F = 0.282$, $p = 0.755$).

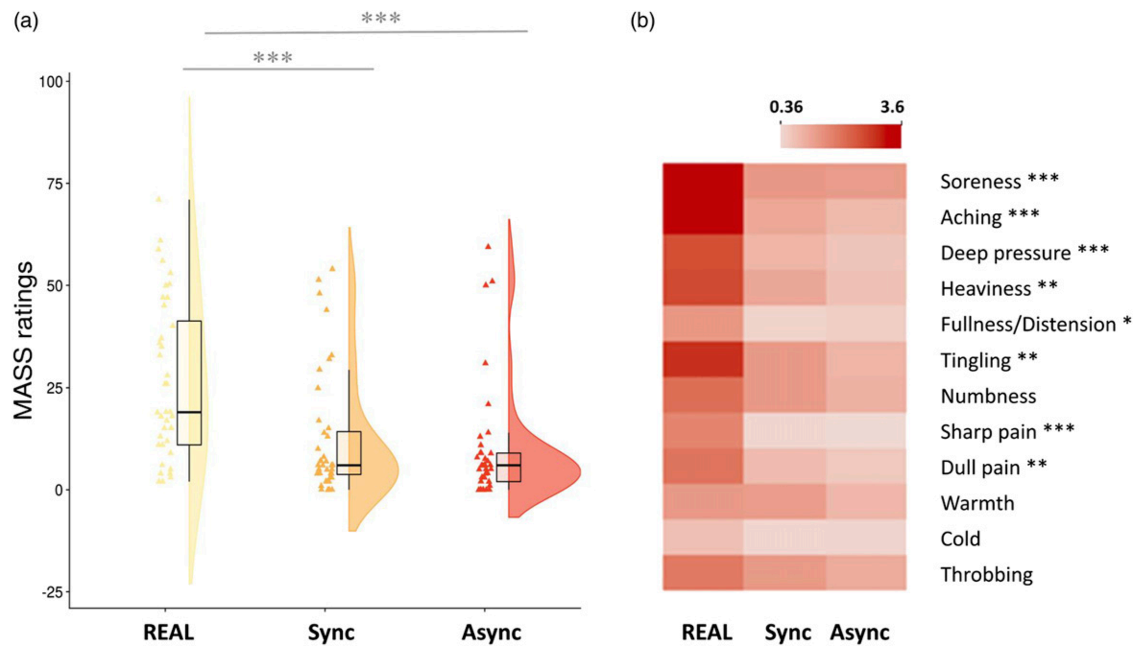

Figure 3. (a) Comparison of *deqi* sensation ratings using the MASS questionnaire. Some *deqi* sensations were also observed under the rubber-hand conditions. The overall *deqi* sensation score under the Sync condition was slightly higher than that under the Async condition, but the difference was not significant ($p = 0.395$). (b) Each MASS questionnaire under three different conditions is represented by heat map. Asterisks indicate significant comparison level (*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$).

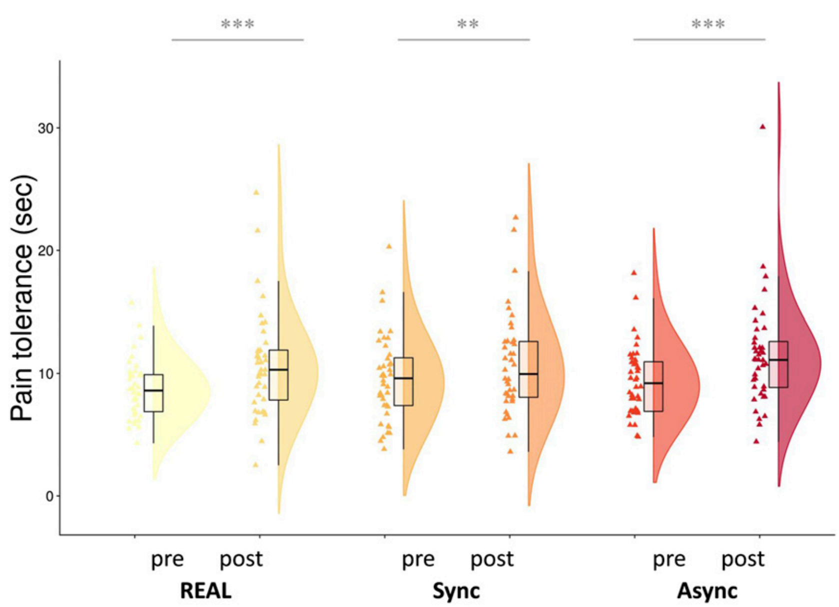

Figure 4. Changes in pain tolerance after acupuncture treatment among the three conditions. After the acupuncture session, the pain tolerance significantly increased in all three conditions. However, no significant time × condition interaction effect and no effect of condition was observed. Error bars indicate standard deviations of the mean; pre: pre-acupuncture; post: post-acupuncture.

Under all conditions, the beta ratio decreased significantly after the acupuncture stimulation. The repeated-measures ANOVA revealed a significant effect of time (F = 43.586, $p < 0.001$), but no effect of condition (F = 2.89, $p = 0.06$) or time × condition interaction was found (F = 0.180, $p = 0.835$).

Under all conditions, the gamma ratio decreased significantly after the acupuncture stimulation. The repeated-measures ANOVA revealed significant effects of time (F = 9.087, $p = 0.003$) and condition (F = 3.50, $p = 0.033$), but no significant time × condition interaction (F = 0.758, $p = 0.471$).

Table 1. Changes in EEG power.

	Real		Sync		Async		ANOVA		
	Pre	Post	Pre	Post	Pre	Post	Time	Condition	Time × condition
Delta	73.20 ± 7.90	81.79 ± 5.41	74.90 ± 8.90	84.25 ± 5.01	74.13 ± 8.76	84.11 ± 5.27	<0.001	0.266	0.835
Theta	12.14 ± 2.67	10.00 ± 2.23	11.67 ± 2.95	8.80 ± 1.70	12.04 ± 4.32	9.02 ± 2.59	<0.001	0.330	0.337
Alpha	9.64 ± 4.33	5.36 ± 2.48	9.67 ± 6.28	4.79 ± 2.94	9.40 ± 5.08	4.78 ± 2.77	<0.001	0.888	0.755
Beta	4.22 ± 4.00	2.41 ± 1.24	3.32 ± 1.55	1.85 ± 1.16	3.36 ± 1.65	1.80 ± 0.92	<0.001	0.060	0.835
Gamma	0.80 ± 1.44	0.44 ± 0.31	0.44 ± 0.20	0.29 ± 0.20	0.47 ± 0.25	0.29 ± 0.18	<0.01	0.033	0.471

Data are reported as power value of EEG activity: percentage (%); pre: pre-acupuncture; post: post-acupuncture.

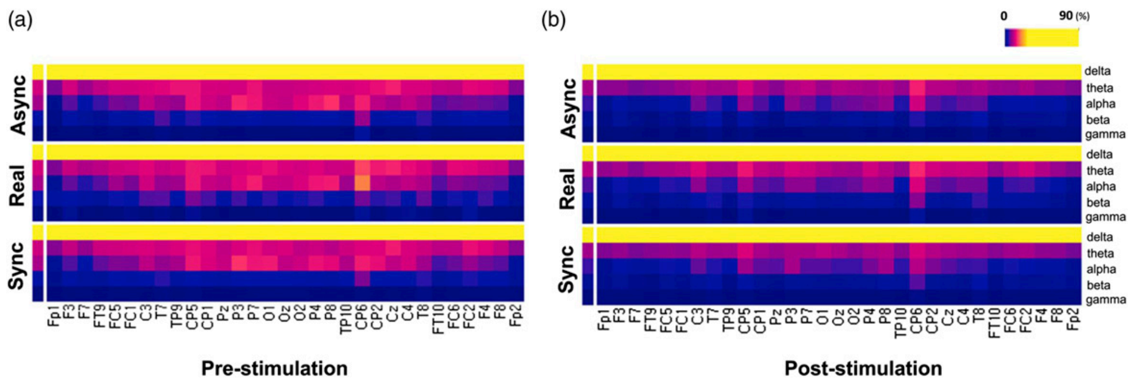

Figure 5. Changes in electroencephalography power. Increased delta and decreased theta, alpha, beta, and gamma waves were observed after acupuncture treatment under all three conditions. The power in each band divided by the overall spectral power was used to compute each power ratio. The brain oscillation patterns in response to acupuncture stimulations were demonstrated across electrodes. The changes in EEG power of each electrodes were visualized using Orange Software (version 3.28.0, https://orangedatamining.com).

Correlation between deqi *sensations and pain tolerance*

We found a significant positive correlation between *deqi* sensations and changes in the pain tolerance under the Sync condition (heaviness: $r = 0.358$, $p = 0.023$; tingling: $r = 0.428$, $p = 0.006$; numbness: $r = 0.404$, $p = 0.01$; warmth: $r = 0.342$, $p = 0.031$), but not under the Async condition.

Correlation between electroencephalography power and pain tolerance

A significant positive correlation between changes in delta power and changes in pain tolerance was observed only under the Real condition ($r = 0.336$, $p = 0.036$). Similarly, a significant negative correlation between changes in beta power and changes in pain tolerance was observed only under the Real condition ($r = 0.351$, $p = 0.028$). Except for these associations of changes in delta and beta power with changes in pain tolerance under the Real condition, EEG power changes were not correlated with changes in pain tolerance.

Discussion

We investigated the effects of three components of acupuncture stimulation (visual, tactile, and body ownership) on acupuncture analgesia using an RHI paradigm. We demonstrated that the pain tolerance was increased after acupuncture treatment applied to the real hand or to the rubber hand. Among the visual, tactile, and body ownership components, expectation of acupuncture treatment sparked by visual information of receiving acupuncture treatment was the predominant factor in acupuncture analgesia. *Deqi* sensations were a contributing factor to acupuncture analgesia when the rubber hand was incorporated with participants' own bodies. Brain oscillation patterns in response to acupuncture treatment were similar regardless of the condition.

In the current study, we demonstrated that acupuncture treatment increased the pain tolerance under all three conditions, i.e. the Real, Sync, and Async conditions. We dissociated the body ownership component from the visual component by comparing the Sync and Async conditions. Increases in experimentally induced heat threshold by acupuncture treatment under both the Sync and Async conditions were similar to that under the Real condition. These findings are consistent with those of previous studies in which the expectation of acupuncture treatment was the one of important factors in acupuncture analgesia.[2,4,6,7] In these previous studies, participants were instructed to focus on videos and imagine themselves being treated, and the findings highlight the importance of credibility in the context of acupuncture treatment. In our experiment, we did not directly induce credibility, but we instructed participants to focus on the rubber hand and acupuncture stimulation. Interviews with participants indicated that this procedure may have influenced participants, facilitating credibility in the acupuncture treatment context.

In our study, we fixed the order of the acupuncture stimulation, scheduling the Real condition on the first day to provide everyone with a similar experience of acupuncture. The fixed-order experimental design might produce expectations of a therapeutic context, resulting in the analgesic effects of the rubber-hand conditions, even the Async condition. Recent studies suggest that prior information about the context can influence pain perception,[29] and pain perception can be predicted based on Bayesian modeling from prior experiences and expectations.[30] Even when patients receive placebo without deception, their body might respond via unconscious prediction induced by the embodied assumption of medication taking.[31] Given that needling on either the real hand or the rubber hand is administered in the context of medical intervention, brain might minimize prediction error and tend to perceive the needling on the rubber hand as acupuncture treatment on their own hand. In the current study, participants experienced *deqi* sensations in response to acupuncture stimulation under either the Sync or the Async condition. Since all participants had experienced analgesic effects of acupuncture in the Real condition on the first day, it is assumed that visual stimuli induced expectations of a therapeutic context might result in analgesic effects in both Sync and Async condition. It suggests that a therapeutic context is crucial in producing analgesic effect of acupuncture with visual component only. Further study will be necessary to investigate the interaction of prior knowledge and visual component of acupuncture in the future.

Accumulating evidence shows that looking at ones' own body reduces pain experience. When looking at their stimulated right hand, painful stimuli applied to that hand were less painful compared to when looking at other objects.[32,33] Mohan et al., showed no changes in pain perception delivered on the real hand during the rubber hand illusion than control condition.[22] In contrast, other studies showed that looking at the incorporated rubber hand led to an increase in pain threshold and reduced discomfort caused by cold stimuli.[34–37] Looking at a virtual body can increase pain threshold similar to looking at one's real body.[14,38] The majority of studies suggest that analgesic effect can be transferable via the visual information of the rubber hand when the hand is incorporated into one's own body image.[39] Looking at the body part, pain stimuli applied to that hand might be rated as being less painful. Therefore, in the current study, after body ownership was manipulated in one hand (i.e. left hand), we measured the changes of the pain tolerance of another hand (i.e. right hand), which was out of sight. This procedure might minimize the analgesic effect of seeing their own body and investigate the role of three components of acupuncture stimulation in acupuncture analgesia using the RHI paradigm.

In the present study, we observed noticeable experience of the *deqi* sensations in response to acupuncture stimulation under both the Sync and Async conditions. In contrast, *deqi* sensations such as heaviness, tingling, numbness, and warmth were significantly correlated with acupuncture analgesia only under the Sync condition. These findings suggest that *deqi* sensations might have been an important factor in acupuncture analgesia when the rubber hand was incorporated with participants' own bodies. Kong et al. found significant correlations of acupuncture analgesia with *deqi* ratings of numbness and soreness.[40] Also, in a study of primary dysmenorrhea, *deqi* sensations were considered a major indicator of the analgesic effect of acupuncture.[41] Furthermore, activation of the insula, a key region in the brain's interoceptive system, was correlated with *deqi* sensations when the rubber hand was incorporated with participants' own bodies.[11] Taken together, these findings suggest that *deqi* sensations might be involved pain reduction induced by the body ownership component of acupuncture under the synchronized rubber-hand condition. Further study will address how *deqi* sensations mediate acupuncture analgesia and how the mediation effects vary across different body ownership conditions.

Changes in brain oscillation may be an important component of the neurophysiological mechanisms behind acupuncture analgesia. Quantitative EEG analysis revealed that brain oscillations in the delta and alpha bands increased under acupuncture treatment.[42] Previous work has shown that mu rhythm power was increased after acupuncture stimulation of the ST36 acupoint compared to control acupoints.[43] Significant changes in the alpha band were found when subjects reported greater *deqi* sensations after acupuncture stimulation of the forearm.[44] Phase coherence in the theta and alpha bands tended to increase after acupuncture stimulation accompanied by *deqi* sensations.[45] In the current study, no significant differences were found in EEG changes between the Real condition and the rubber-hand conditions. Under all three conditions, delta waves increased while theta, alpha, beta, and gamma waves decreased after acupuncture stimulation, which could be attributed to a relaxation state following acupuncture stimulation. It is well known that increases in slow EEG waves are related to a stable, near-sleeping state, whereas increases in faster EEG waves are associated with higher levels of thought, attention, or tension.[46] As previously reported, relaxation and vigilance after acupuncture treatment were associated with autonomic nervous system and brain oscillation patterns.[27] Furthermore, a pain-induced gamma wave was significantly reduced after acupuncture treatment.[47] Taken together, these findings indicate that enhanced slow waves and decreased fast waves following acupuncture treatment might be derived from relaxation states due to the expectation of acupuncture treatment. Notably, the present study demonstrated that enhanced delta and reduced beta waves in response to acupuncture treatment were correlated with acupuncture analgesia only in the real-hand condition, not in the rubber-hand conditions. Changes in delta and beta waves were more closely associated with acupuncture analgesia in participants' own bodies. Further study will be necessary to identify different mechanisms underlying these three components of acupuncture analgesia.

Notably, we compared pain reduction from acupuncture treatment using a RHI paradigm to separate multisensory elements of acupuncture treatment and clarified the roles of three components of acupuncture analgesia. Under the real-hand condition, acupuncture treatment can induce pain reduction by visual, tactile, and body ownership components. Under the rubber-hand conditions, acupuncture analgesia was induced by visual and body ownership elements under the synchronized condition, whereas it was only induced by the visual component under the asynchronized condition. Interestingly, *deqi* sensations were noticeable in both the Sync and Async conditions. Independent of body ownership, visual information can generate a therapeutic context and successfully induce *deqi* sensations even under an asynchronized condition. Our results support previous findings indicating that top-down components of acupuncture treatment should be considered to understand the neural mechanisms of acupuncture analgesia.

Acupuncture treatment involves somatosensory components as well as cognitive components, including attention, expectations of treatment, and medical context.[48] Not only bottom-up components of needling but also top-down components of acupuncture can contribute to acupuncture analgesia. The acupuncture stimulations on the rubber hand in the current study are expected to boost the placebo effect by inducing visual expectation, which would ultimately result in acupuncture analgesia. In the current study, we discovered that the visual anticipation plays a significant influence in acupuncture analgesia. When a body part is the focus of attention, sensory signals may "burst out" and become conscious, which would cause them to be regarded as novel sensations.[49,50] Through descending modulatory activities, attention reveals a tingling sensation by opening the door for repressed or ectopic sensory information.[51] Perceptual experiences arise from higher cognitive processes independently of sensory stimuli.[52] For instance, a rubber hand can elicit tingling feelings.[53] Furthermore, participants have similar experiences to real laser acupuncture even with fake laser acupuncture, which delivers no physical stimulus.[54] In our earlier study, participants who were exposed to the expectation of cutaneous electrical stimulation experienced more deqi sensation.[55] These results were linked to the brain's salience network, which plays a predictive role.[55] According to the predictive coding paradigm, the perception is generated using a hierarchical system that evaluates ascending and descending information (prior expectations), with the goal of minimizing the discrepancy between predicted and incoming signals.[56] Descending brain modulation works together to produce sensory sensations from acupuncture stimulation in addition to simple needling.[11] Therefore, it is assumed that higher cognitive processes, such as attention and visual expectancies, contribute considerably to the generation of *deqi* experience and acupuncture analgesia in both the Sync and Async situations of the current experiments.

This study had several limitations. First, we did not include a no-treatment control group without the rubber-hand illusion. Therefore, we cannot fully exclude the effects of habituation or sensitization on the pain tolerance in this study. The pain tolerance was not significantly increased between the pre-treatment and post-treatment in no treatment control in our previous study (8.33 ± 2.02 vs 8.83 ± 2.57, $t = 1.62$, $p > 0.05$), indicating that there might be no habituation or sensitization on the pain tolerance in this study.[15] However, we cannot fully exclude other psychosocial factors or other components such as the therapeutic alliance between practitioner and the patients.[57] Second, participants completed the Real condition first in a fixed order. Thus, all participants received the same acupuncture stimulation to their hands and experienced similar acupuncture analgesia. This might have minimized the confounding effects of acupuncture experience. However, we randomized the Sync and the Async conditions and can therefore exclude the order effect of body ownership in this experiment. And we observed no significant differences of increased pain tolerance between their visit order (day 2 or day 3) in the Sync and the Async conditions. Lastly, the washout period might be crucial for the evaluation of pain threshold. The experiments were carried out over three separate days. The interval between each experiment was at least 2 days. Pretreatment pain thresholds for the three treatments did not differ substantially according to an ANOVA test (Real: 8.75 ± 0.38, Sync: 9.57 ± 0.56, Async: 9.37 ± 0.46, $F = 0.939$, $p = 0.396$). We can therefore infer that the current study's within-subjects cross-over design can guarantee a sufficient washout duration for determining the experimental pain threshold.

In conclusion, we clarified the components of acupuncture stimulation in acupuncture analgesia through a multisensory integration paradigm. Expectation of acupuncture treatment sparked by visual information of receiving acupuncture treatment was the one of important factors in acupuncture analgesia in our study. This study is a first step toward separating various components of acupuncture analgesia and utilizing those components to maximize the analgesic effect.

Author contributions

D.H.C Conceptualization; Methodology; Writing – original draft; S.Y.L Data curation; Methodology; Writing – review and editing; I.S.L Data curation; Methodology; Supervision; Writing – review and editing; Y.C Conceptualization; Data curation; Funding acquisition; Investigation; Supervision; Writing – original draft.

Declaration of conflicting interests

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Data availability

Data available on request from the authors.

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Supplemental Material

Supplemental material for this article is available online.

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