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When pain is not only pain: Inserting needles into the body evokes distinct reward-related brain responses in the context of a treatment

In-Seon Lee [a,b], Christian Wallraven [c], Jian Kong [d], Dong-Seon Chang [e], Hyejung Lee [a], Hi-Joon Park [a], Younbyoung Chae [a,c,*]

[a] Acupuncture and Meridian Science Research Center, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
[b] Department of Internal Medicine: Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen, Tübingen, Germany
[c] Department of Brain Cognitive Engineering, Korea University, Seoul, Republic of Korea
[d] Department of Psychiatry, Massachusetts General Hospital, Charlestown, MA, USA
[e] Department of Human Perception, Cognition and Action, Max Planck Institute for Biological Cybernetics, Tübingen, Germany

HIGHLIGHTS

- Acupuncture yielded greater brain activation in reward-related area in the context of treatment.
- Inserting needles into the body in the context of treatment modulated pain responses in the brain.
- Pain induced by therapeutic tools is modulated differently by the power of context in medical practice.

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ABSTRACT

The aim of this study was to compare behavioral and functional brain responses to the act of inserting needles into the body in two different contexts, treatment and stimulation, and to determine whether the behavioral and functional brain responses to a subsequent pain stimulus were also context dependent. Twenty-four participants were randomly divided into two groups: an acupuncture treatment (AT) group and an acupuncture stimulation (AS) group. Each participant received three different types of stimuli, consisting of tactile, acupuncture, and pain stimuli, and was given behavioral assessments during fMRI scanning. Although the applied stimuli were physically identical in both groups, the verbal instructions differed: participants in the AS group were primed to consider the acupuncture as a painful stimulus, whereas the participants in the AT group were told that the acupuncture was part of therapeutic treatment. Acupuncture yielded greater brain activation in reward-related brain areas (ventral striatum) of the brain in the AT group when compared to the AS group. Brain activation in response to pain stimuli was significantly attenuated in the bilateral secondary somatosensory cortex and the right dorsolateral prefrontal cortex after prior acupuncture needle stimulation in the AT group but not in the AS group. Inserting needles into the body in the context of treatment activated reward circuitries in the brain and modulated pain responses in the pain matrix. Our findings suggest that pain induced by therapeutic tools in the context of a treatment is modulated differently in the brain, demonstrating the power of context in medical practice.

1. Introduction

Pain, according to the International Association for the Study of Pain, is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [1]. Pain is considered a treatment target because of negative effects on patients' quality of life, including its role as a stressor on emotion and cognitive functions [2–4]. Pain impairs important cognitive functions by interrupting attention [5] and attenuating the value of rewards [6]. Pain, usually opposed to reward, has generally been regarded as negative, with only a few exceptions in the context of supporting survival. However, some recent research has emphasized the positive value of pain. Benedetti et al. [7] showed that participants produced greater pain tolerance when they informed that ischemic arm pain would be beneficial to the muscles, suggesting that pain could also be regarded as a reward when enduring pain was a benefit to participants. Leknes

* Corresponding author at: Acupuncture and Meridian Science Research Center, College of Korean Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul 130-701, Republic of Korea.
E-mail address: ybchae@khu.ac.kr (Y. Chae).

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et al. [8] demonstrated that sympathetic activity and brain activity in pain matrix were significantly attenuated when moderate pain was perceived as pleasant, indicating that the associated context was important for the perception of pain. Other studies have shown how participants' valence ratings (positive or negative) and stimuli recognition ratings (pleasant or painful) were influenced by the context (relative relief or control) in which they received the pain, even when the same degree of pain was delivered [9,10].

What about pain induced by therapeutic tools and devices? Many therapeutic tools, such as surgery devices, dental instruments, injection syringes, or acupuncture needles, trigger negative associations and reactions related to pain. Still, most patients seem to endure the pain induced by these therapeutic tools without much complaint, though their reaction would most likely be very different if the same pain (with the same tools) was induced in a different context, e.g., as a torture method during an interrogation. This demonstrates not only that the context of a treatment is important but also that pain induced by therapeutic tools might be associated with reward values because patients would have no reason to undergo painful treatments unless they believed that the expected value of reward (relief from the initial suffering or pain) outweighs the additional pain induced by the treatment. From a physiological point of view, inserting needles into the body is generally considered a painful stimulus, but from a therapeutic point of view, inserting needles into the body during acupuncture is known to result in various clinical and therapeutic effects, such as acupuncture analgesia [11,12]. If acupuncture needling is delivered outside of a therapeutic context, we imagine that it would be considered a painful 'stimulus' for the patient, which might cause different physiological responses than acupuncture 'treatment' given in a therapeutic context. We were able to test 1) whether the same act of inserting needles into the body in two different contexts (stimulation and treatment) would result in different behavioral and functional brain responses and 2) whether inserting needles into the body affected the behavioral and functional brain responses to a subsequent pain stimulus (i.e., analgesic treatment effects) differently depending on context. Acupuncture as a test model was also favorable because the behavioral and neural responses to acupuncture needle stimulation have already been extensively studied in various placebo- and expectancy-controlled setups, allowing a generally good and robust interpretation of brain imaging data [11,13–15].

In the present study, we investigated whether inserting needles into the body (acupuncture) led to different behavioral and brain responses in different contexts (stimulation vs. treatment) and whether the manipulation of these two contexts led to distinct pain modulation responses to a subsequent pain stimulus. We gave two groups of participants with different instructions regarding the study, and we measured subjective pain ratings and brain responses to acupuncture and to a subsequent pain stimulus using questionnaires and functional magnetic resonance imaging (fMRI). We hypothesized that inserting needles into the body in a therapeutic context would be more likely to activate reward-related brain regions (e.g., the ventral striatum) than in the context of providing stimulation. We also hypothesized that context manipulation would lead to differences in pain-processing regions of the brain, evoking distinct patient responses to a subsequent pain stimulus.

2. Materials and methods

2.1. Participants

Twenty-four healthy volunteers were included in this study (7 females, aged 19–36, mean = 23.6, standard error = 0.8). All volunteers were recruited using advertisement posters on bulletin boards at Korea University and Kyung Hee University, Seoul, Republic of Korea. All participants were right-handed. None of the participants had pain disorders; a history of neurological, psychiatric, or visual disorders; or contraindications to MRI. They were prohibited from using alcohol, caffeine, or any other drugs or medications on the day of the experiment. All participants received a detailed explanation of the study and provided written informed consent. This experiment conformed to the guidelines of the Declaration of Helsinki and was approved by the Korea University's Institutional Review Board.

2.2. Group allocations

All participants were randomly allocated to either the acupuncture treatment (AT, n = 12) group or the acupuncture stimulation group (AS, n = 12) using a computer program (Random Allocation Software, RevolutionAnalytics.com) separately for each sex. All stimuli (tactile, acupuncture, and pain) were applied identically to all participants, but different instructions were given to manipulate the participants' understanding of acupuncture.

The AT group was informed about the analgesic effects of acupuncture treatment and was told that the purpose of the study was to evaluate these analgesic effects. Participants were told that in quantitative sensory tests, measured thermal pain dropped by 30% following acupuncture treatments. The AS group was only informed about the three different types of stimuli (tactile, acupuncture and pain), and told that the purpose of the study was to evaluate brain responses to the three different stimuli. They were not informed of the analgesic effects of acupuncture treatment.

2.3. Study design

2.3.1. Day 1: instruction and familiarization

On Day 1, participants were informed about the purpose of the study and the different types of stimuli they would receive: tactile (touch on the hand), acupuncture (inserting needles into the foot), and pain (thermal pain on the hand and mechanical pain on the foot). Only the context of acupuncture stimulation was explained differently to each group. Participants spent time getting familiarized with the stimuli and rating methods while receiving tactile, acupuncture and pain stimuli according to the quantitative sensory testing (QST) standardized protocol [16].

2.3.2. Day 2: behavioral assessment

On Day 2, all participants filled out the Acupuncture Expectancy Scale (AES) and Acupuncture Fear Scale (AFS) questionnaires [17–19]. Then, anticipation of pain induced by acupuncture needle penetration was assessed using an 11-point Verbal Numerical Rating Scale (VNRS). For psychophysical assessments, participants received tactile and mechanical pain stimuli and rated pain sensations using an 11-point VNRS (0 = not at all, 10 = most intense pain imaginable).

2.3.3. Day 2: fMRI sessions

All participants underwent two consecutive fMRI sessions for 7 min each. The first session consisted of tactile + pain stimulation (T + P), and the second session consisted of acupuncture + pain stimulation (A + P). The order of the two sessions was randomized separately for each group. In T + P sessions, tactile stimulation (T) was delivered to the participant's hand and mechanical pain stimulation (P) to the foot. The order of the stimulations was as follows: 60 s resting, 20 s tactile stimulation, 20 s resting, 20 s pain stimulation. In the A + P session, acupuncture stimulation (A) was delivered to the participant's hand and mechanical pain stimulation (P) to the foot, with the order of stimulations as follows: 60 s resting, 20 s acupuncture stimulation, 20 s resting, 20 s pain stimulation (Fig. 1). After each session, participants were asked to rate the sensation of pain using an 11 point VNRS (0 = not at all, 10 = most intense pain imaginable).