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CEREBRAL BLOOD FLOW-BASED EVIDENCE FOR MECHANISMS OF LOW- VERSUS HIGH-FREQUENCY TRANSCUTANEOUS ELECTRIC ACUPOINT STIMULATION ANALGESIA: A PERFUSION FMRI STUDY IN HUMANS

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Abstract—Brain activities in response to acupuncture have been investigated in multiple studies; however, the neuro-mechanisms of low- and high-frequency transcutaneous electric acupoint stimulation (TEAS) analgesia are unclear. This work aimed to investigate how brain activity and the analgesic effect changed across 30-min low- versus high-frequency TEAS. Forty-six subjects received a 30-min 2, 100-Hz TEAS or mock TEAS (MTEAS) treatment on both behavior test and functional magnetic resonance imaging (fMRI) scan days. On the behavior test day, the pain thresholds and pain-related negative emotional feeling ratings were tested five times – at 4.5 min before treatment, at 10, 20, and 30 min during treatment and 4.5 min after the treatment. On the fMRI scan day, to match the time-points in the behavioral testing session, the cerebral blood flow (CBF) signals were collected and incorporated with five independent runs before, during and after the treatment, each lasting 4.5 min. The analgesic effect was observed in both the TEAS groups; the analgesic affect was not found in the MTEAS group. The effect started at 20 min during the treatment and was maintained until the after-treatment states. In both TEAS groups, the regional CBF revealed a trend of early activation with later inhibition; also, a positive correlation between analgesia and the regional CBF change was observed in the anterior insula in the early stage, whereas a negative relationship was found in the parahippocampal gyrus in the later stage. The TEAS analgesia was specifically associated with the default mode network and other cortical regions in the 2-Hz TEAS group, ventral striatum and dorsal anterior cingulate cortex in the 100-Hz TEAS group, respectively. These findings suggest that the mechanisms of low- and high-frequency TEAS analgesia are distinct and partially overlapped, and they verify the treatment time as a notable factor for acupuncture studies.

Key words: frequency, acupuncture analgesia, transcutaneous electric acupoint stimulation, cerebral blood flow.

INTRODUCTION

Acupuncture is gaining widespread popularity, and its analgesic effect has been consistently reported (Sim et al., 2002; Sun et al., 2008; Molsberger et al., 2010; Han, 2011). Compared to traditional manual acupuncture, electroacupuncture (EA) or transcutaneous electric acupoint stimulation (TEAS) has the advantage of the precision of stimulation parameters, high reproducibility of the therapeutic effects and significant reduction in labor. The popularity of these new modalities of acupuncture has increased. Different frequencies were used for EA and TEAS. Although both are effective for pain-relief (Han, 2011; Xiang et al., 2012), low- and high-frequency stimuli could treat specific dysfunctions. Low-frequency EA was specifically recommended for muscular atrophy (Liu, 1998), and high-frequency EA was specifically effective in treating spinal spasticity (Yuan et al., 1993). For treating drug abuse, EA/TEAS at high frequency was shown to reduce withdrawal syndrome better, whereas low frequency was preferred for the suppression of psychic dependence (Cui et al., 2008). In basic animal research, low- and high-frequency EA/TEAS could facilitate the release of endogenous opioid peptides, and the difference was that the former was mediated by the μ and δ opioid receptors, whereas the latter was mediated by the κ opioid receptor (Han, 2003). Investigations on its brain mechanisms had been limited in humans until the recent development of noninvasive neuroimaging techniques, especially functional magnetic resonance imaging (fMRI).

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Abbreviations: ANOVA, analysis of variance; ASL, arterial spin labeling; BOLD, blood oxygen-dependent level; CBF, cerebral blood flow; DMN, default mode network; EA, electroacupuncture; fMRI, functional magnetic resonance imaging; FOV, field of view; MTEAS, mock TEAS; ROI, region of interest; TEAS, transcutaneous electric acupoint stimulation; VAS, visual analog scale.

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Only a few studies have tried to investigate the brain activity changes induced by low- versus high-frequency EA/TEAS in humans. Zhang et al. first reported a significant correlation between the blood oxygen-dependent level (BOLD) signal intensity and the extent of analgesia in some brain areas induced by 2- vs. 100-Hz TEAS, by using a model including a 6-min block-designed fMRI scan as well as pain threshold tests before and after 30-min TEAS (Zhang et al., 2003a,b). Another study revealed that 2- and 100-Hz EA, especially 2 Hz, produced more widespread fMRI signal increase than manual acupuncture (Napadow et al., 2005). On the basis of the above research, the brain regional activations induced by EA/TEAS were only focused on short-period treatment, and the time dependency factor in the development of the treatment effect was considered only to a lesser degree. As far as we are aware, 20–45 min acupuncture treatment has been conventionally used in clinical practice (Sim et al., 2002; Cui et al., 2008; Ahsin et al., 2009; Molsberger et al., 2010; Unterrainer et al., 2010), and a relatively long treatment period showed a better analgesic effect than a short treatment period (Ulett et al., 1998; Cheing et al., 2003). In a 31-min EA block-designed fMRI study, the results of the first- and last-3 blocks were different (Napadow et al., 2009). More recently, we found that the cerebral blood flow (CBF) decreased globally and in some areas, including the limbic region as well as in the somatosensory brain regions following a 30-min 2-Hz TEAS; this finding is different from the somatosensory-activation results in most short-period acupuncture research (Wu et al., 2002; Zhang et al., 2003a,b; Bai et al., 2009; Hui et al., 2010). These studies implied that the brain activities in response to short- and long-period acupuncture might be different.

In this study, we addressed three research questions. How does the time course of brain activity change across a 30-min TEAS? Which brain region plays a critical role in analgesia at different treatment stages? Based on these two questions, are there any frequency-dependent findings that imply different analgesic mechanisms between low- vs. high-frequency TEAS? Arterial spin labeling (ASL) perfusion fMRI was employed in this work to measure the CBF in each time period; it has displayed excellent reproducibility over a long period of time and less between-subject variability compared to BOLD fMRI (Aguirre et al., 2002; Wang et al., 2003b; Wang et al., 2003a). A combined fMRI scanning and behavior-testing model was applied (Fig. 1) in this study, and the pain thresholds and time-matched CBF signals were collected before, during and after 30-min TEAS treatments.

EXPERIMENTAL PROCEDURES

Subjects

Fifty-two healthy, right-handed participants naïve to acupuncture (27 males, mean age 23 years, range 19–28) were enrolled in this experiment, and no female subject was having a menstrual period. All the subjects signed informed consent to the purposes, procedures and potential risks of this study and were free to withdraw from the experiment at any time. The research procedures were approved by the ethics committee of the Peking University, and the experiments were conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the British Medical Journal (18 July 1964).

Experiment procedures

The subjects were recruited to participate in one behavioral testing session and one fMRI scanning session. The two sessions were set in random order and separated by a minimum of one week. The 52 subjects were randomized into one of three groups, receiving mock TEAS (MTEAS), 2-Hz TEAS or 100-Hz TEAS.

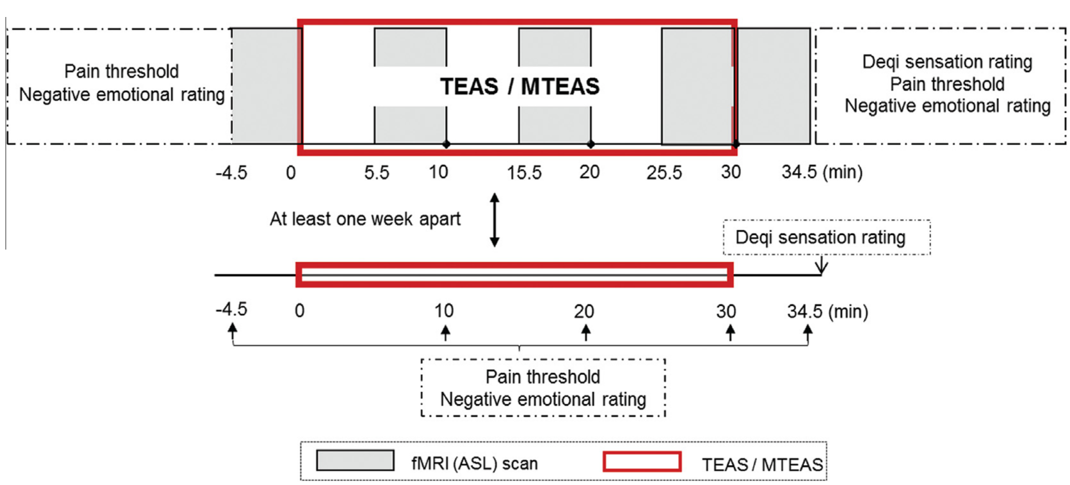

Fig. 1. Details of experimental procedure. The subjects received a 30-min TEAS/MTEAS treatment on both the fMRI scan day and the behavior test day. On the fMRI scan day, functional scanning incorporated with five independent runs, each lasting 4.5 min, as follows: beginning at 4.5 min before; 5.5, 15.5 and 25.5 min during; and immediately after the treatment. The pain threshold and the associated negative emotional rating were tested before and after the whole scans. On the behavior test day, pain thresholds and the negative emotional ratings were tested five times as follows: at 4.5 min before; 10, 20 and 30 min during; and 4.5 min after the treatment. Moreover, the feelings of *'deqi'* were collected on both days after the last pain threshold measurement.