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Enhancing treatment of osteoarthritis knee pain by boosting expectancy: A functional neuroimaging study

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A R T I C L E I N F O

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A B S T R A C T

Objectives: Expectation can significantly modulate pain and treatment effects. This study aims to investigate if boosting patients' expectancy can enhance the treatment of knee osteoarthritis (KOA), and its underlying brain mechanism.
Methods: Seventy-four KOA patients were recruited and randomized to three groups: boosted acupuncture (with a manipulation to enhance expectation), standard acupuncture, or treatment as usual (TAU). Each patient underwent six treatments before being debriefed, and four additional treatments after being debriefed. The fMRI scans were applied during the first and sixth treatment sessions.
Results: We found significantly decreased knee pain in the boosted acupuncture group compared to the standard acupuncture or TAU groups after both six and ten treatments. Resting state functional connectivity (rsFC) analyses using the nucleus accumbens (NAc) as the seed showed rsFC increases between the NAc and the medial prefrontal cortex (MPFC)/rostral anterior cingulate cortex (rACC) and dorsolateral prefrontal cortex in the boosted group as compared to the standard acupuncture group after multiple treatments. Expectancy scores after the first treatment were significantly associated with increased NAc-rACC/MPFC rsFC and decreased knee pain following treatment.
Conclusions: Our study provides a novel method and mechanism for boosting the treatment of pain in patients with KOA. Our findings may shed light on enhancing outcomes of pharmacological and integrative medicines in clinical settings.

1. Introduction

Non-specific effects, such as the placebo effect, play an important role in medical practice (Finniss et al., 2010; Price et al., 2008). Under certain circumstances, such as clinical trials, it presents challenges for investigators. In other circumstances, it can enhance treatment outcomes (Gollub and Kong, 2011; Weiss and Swede, 2016). While the placebo effect is well accepted, there is still much to learn about its underlying mechanism and how to harness it in clinical settings.

It is believed that expectation plays an important role in non-specific effects, particularly in the placebo effect (Amanzio and Benedetti, 1999; Amanzio et al., 2013; Atlas et al., 2012; Tracey, 2010). Investigators have found a well-accepted expectancy manipulation model (Eippert et al., 2009; Hashmi et al., 2014; Kong et al., 2006, 2009a; Wager et al., 2004), in which they surreptitiously reduce stimulus intensity after placebo treatment to make subjects believe the treatment is effective, that can produce greater placebo effects compared to verbal suggestion alone (Colloca et al., 2008; Kong et al., 2013b; Voudouris et al., 1990). In addition, this model can also enhance the effect of active treatments in healthy volunteers (Bingel et al., 2011; Kong et al., 2009a). Nevertheless, few studies have applied the expectancy manipulation model on the chronic pain patient population due to the

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difficulty in manipulating chronic pain intensity compared to experimental pain. In this study, we first applied an expectancy model using experimental heat pain to enhance subjects' expectation of acupuncture analgesia, and then tested whether this enhanced expectation improved the treatment effect of acupuncture on chronic pain caused by knee osteoarthritis (OA).

Although still under investigation, one potential neural mechanism by which enhanced expectation may lead to improved therapeutic outcomes is through the engagement of the reward system in the brain. Using pain as an example, the expectation of treatment effect (pain relief) can be rewarding and pleasurable, thus expectation, in the context of treatment in clinics, can be regarded as a special case of reward (Leknes and Tracey, 2008; Petrovic et al., 2005; Scott et al., 2007; Yu et al., 2014b). In support of this hypothesis, neuroimaging studies have found that the reward system, particularly the nucleus accumbens (NAc), is involved in mediating placebo effects in patients with Parkinson's disease (de la Fuente-fernandex et al., 2002), depression (Mayberg et al., 2002), anxiety (Petrovic et al., 2005), and pain (Scott et al., 2007; Yu et al., 2014b).

Literature suggests that two neurotransmitter systems are involved in the pain modulation of reward expectation and motivation: the dopamine system increases motivation, whereas the opioid system influences motivation indirectly by modulating subjective feelings of pain and reward (Berridge, 2007; Navratilova et al., 2015a; Navratilova and Porreca, 2014). Studies also found that the two systems are closely related neuroanatomically, and interact in complex ways (Leknes and Tracey, 2008). The brain regions that are particularly well-situated to mediate interactions between the two systems are the NAc (Schmidt et al., 2014; Smith and Berridge, 2007; Szechtman et al., 1981; Wei et al., 2004; Zubieta et al., 2001), anterior cingulate cortex (ACC), and medial prefrontal cortex (MPFC) (Hare et al., 2008; Navratilova et al., 2015a, 2015b; Tuominen et al., 2012).

Recent studies have demonstrated that resting state functional connectivity (rsFC) can provide information about the intrinsic functional organization of the brain (Fox and Raichle, 2007; Vincent et al., 2006), improve our understanding of pain modulation (Kong et al., 2013a), and predict treatment outcomes (Tetreault et al., 2016). In this study, we investigated 1) if boosted expectancy of acupuncture analgesia for experimental pain can enhance acupuncture treatment for knee OA and 2) how boosted expectancy modulates rsFC of the NAc. We chose acupuncture treatment of chronic pain because it provides an excellent model for studying the modulation effect of expectation. Studies indicate that the non-specific effect of acupuncture is robust (Cherkin et al., 2009; Vickers et al., 2012). Furthermore, acupuncture is gaining popularity due to its total clinical effectiveness (Berman et al., 2010; Vickers and Linde, 2014), and rarity of adverse effects (Melchart et al., 2004; White et al., 2001). We hypothesized that acupuncture with boosted expectancy would 1) produce greater clinical improvements than acupuncture alone and 2) increase rsFC between the NAc and rACC/MPFC.

2. Materials and methods

2.1. Subjects

Subjects with knee OA were recruited. Experiments were conducted with approval from the Massachusetts General Hospital Institutional Review Board and with the written, informed consent of each participant. All subjects agreed to allow their data to be analyzed. The study was registered at clincaltrials.gov (NCT#: 01040754).

Inclusion criteria included: between 40 and 70 years of age; met the Classification Criteria of the American College of Rheumatology for osteoarthritis of the right and/or left knee; radiographic evidence of Grade 2 or 3 knee OA using the Kellgren-Lawrence Scale. Exclusion criteria were: interventional procedure for knee pain within two months, including corticosteroid injections to the knee; intent to undergo surgery during the time of involvement in the study; presence of a cardiovascular, neurological or psychiatric disorder; additional pain disorder with severity greater than knee OA pain; pregnancy; acupuncture treatment within one year; difficulties reading, speaking or understanding English. All subjects were told to maintain their baseline medications and other treatments for their knee OA during the duration of the study. They were prompted to report any changes in treatment, including frequency of prn medications, at each study visit.

2.2. Experimental procedure

Subjects were stratified by gender and the most affected knee, and then randomized into one of three groups: boosted acupuncture, standard acupuncture, or treatment as usual (TAU control) at the beginning of session 2 (Supplementary Fig. 1). The randomization table was created by a study biostatistician using the R program. Both acupuncture groups received identical acupuncture treatments for four weeks (2 times/week for the first two weeks, and 1 time/week for the last two weeks). After a mid-point evaluation and debriefing, patients received an additional 4 weeks of acupuncture (1 time/week).

All subjects in the two acupuncture groups participated in a total of 13 study visits, including the baseline training and clinical assessment (session 1), first fMRI scan session including the first acupuncture treatment (session 2), four acupuncture treatments (session 3–6), second fMRI scan session including the sixth acupuncture treatment (the procedure was identical to the first MRI scan) and debriefing at the end of the session in the boosted acupuncture group (session 7), midpoint clinical assessment (session 8), 4 additional acupuncture treatments over the course of a month (session 12), and final clinical assessment (session 13) (Supplementary Fig. 1). In the boosted acupuncture group, an expectancy manipulation similar to our previous studies (Hashmi et al., 2014; Kong et al., 2006, 2009a, 2009b) was applied during the fMRI scan sessions (during treatment one and treatment six) to enhance subjects' positive expectation of pain reduction with acupuncture treatment.

The TAU group participated in 5 visits, including the baseline training and assessment, first fMRI scan, second fMRI scan, midpoint assessment, and a final assessment. They followed the exact timing for the acquisition of behavioral, clinical and imaging data, but without any treatment (Supplementary Fig. 1).

Session 1 was a training and baseline clinical outcome measurement session. Following being screened and signing the consent form, all subjects completed the Knee Injury and Osteoarthritis Outcomes Score (KOOS) to measure their knee pain and function.

A 1×3 grid was drawn on the medial surface of the affected knee, avoiding the patella. Then, calibrated thermal heat pain stimuli were delivered to the medial side of the affected knee using a PATHWAY system with a 3 cm × 3 cm probe (Egorova et al., 2015b; Egorova et al., 2015c). Each stimulus was initiated at a 32 °C baseline and increased to a target temperature that was presented for 12 s, including 2.5 s to ramp up and ramp down. The inter-stimulus interval ranged from 24 to 30 s. Subjects rated their pain for each stimulus during the inter-stimulus interval using a 0–20 Gracely Sensory Box scale (Gracely et al., 1978a, 1978b).

Similar to our previous studies (Hashmi et al., 2014; Kong et al., 2006, 2009a, 2009b), subjects first experienced one ascending series of calibrated heat stimuli. The first stimulus of each ascending series was initiated from a target temperature of 38°C. Subsequent stimuli were increased by 1 °C to 52 °C or to the subject's tolerance: a rating of ~17 (Very Intense) on the Gracely Scale. Two temperatures, one that elicited low ratings (5–7; mild to moderate) and one that elicited high ratings (14–15; strong) were selected for each subject. Once the two temperatures for a subject were determined, he or she was tested for rating response consistency. Random sequences of 4 low and 4 high intensity noxious stimuli were administered. The temperatures were further adjusted as needed. Subjects had to consistently rate the high intensity