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Repeated verum but not placebo acupuncture normalizes connectivity in brain regions dysregulated in chronic pain

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ABSTRACT

Acupuncture, an ancient East Asian therapy, is aimed at rectifying the imbalance within the body caused by disease. Studies evaluating the efficacy of acupuncture with neuroimaging tend to concentrate on brain regions within the pain matrix, associated with acute pain. We, however, focused on the effect of repeated acupuncture treatment specifically on brain regions known to support functions dysregulated in chronic pain disorders. Transition to chronic pain is associated with increased attention to pain, emotional rumination, nociceptive memory and avoidance learning, resulting in brain connectivity changes, specifically affecting the periaqueductal gray (PAG), medial frontal cortex (MFC) and bilateral hippocampus (Hpc). We demonstrate that the PAG–MFC and PAG–Hpc connectivity in patients with chronic pain due to knee osteoarthritis indeed correlates with clinical severity scores and further show that verum acupuncture-induced improvement in pain scores (compared to sham) is related to the modulation of PAG–MFC and PAG–Hpc connectivity in the predicted direction. This study shows that repeated verum acupuncture might act by restoring the balance in the connectivity of the key pain brain regions, altering pain-related attention and memory.

1. Introduction

In recent years, acupuncture has gained popularity in Western medicine in part due to successful treatment of chronic pain (White, 2009). Despite its increasingly widespread use by the general population, clinical trials evaluating the efficacy of acupuncture report inconsistent results. Often they show the general advantage of acupuncture over other physical interventions (Corbett et al., 2013; Manyanga et al., 2014; Vickers and Linde, 2014). The lack of understanding of the underlying mechanisms of acupuncture and reported cases of a failure to elicit greater clinical improvement compared to sham acupuncture (Hinman et al., 2014; Kong et al., 2013; Langevin et al., 2011), however, have hampered incorporation of this treatment modality into mainstream medical practice.

Functional neuroimaging investigation into the mechanisms of acupuncture shows that acupuncture needle stimulation is associated with fMRI signal increase in the insula, thalamus, and primary and secondary somatosensory cortices, signal decrease in the caudate, posterior cingulate cortex, thalamus and parahippocampus, as well as both signal increase and decrease in the medial prefrontal cortex (mPFC), anterior cingulate, amygdala and cerebellum (Chae et al., 2013). In addition, connectivity between these pain regions and the periaqueductal gray (PAG) is modulated during acupuncture (Zyloney et al., 2010) and differentiates verum (genuine) and sham treatments. However, to date neuroimaging studies focused on either the brain regions responding to acute pain sensation and/or measured resting state changes during or immediately after an acupuncture session. Long-term treatment effects and changes in brain regions associated with chronic pain remain unknown. In parallel, substantial effort has gone into identifying the brain regions and networks that show significant changes during the transition from acute to chronic pain (Apkarian et al., 2011; Hashmi et al., 2013), associated, inter alia, with long-term pain learning (Mansour et al., 2014). Most often the medial frontal cortex (MFC) (Baliki et al., 2011, 2014; Cauda et al., 2014; Mutso et al., 2013) and bilateral hippocampus (Hpc) (Gondo et al., 2012; Lang et al., 2009; Mutso et al., 2013; Ploghaus et al., 2001; Vachon-Presseau et al., 2013) are implicated. These brain regions appear to be the hubs involved in pain perception (Gondo et al., 2012; Salomons et al., 2007), placebo analgesia (Eippert et al., 2009; Wager et al., 2007), pain-related memory and emotion (Lang et al., 2009; Ploghaus et al., 2001), and as such control pain perception and modulation.

Of special relevance is the connectivity between the MFC, Hpc and the PAG. While both MFC and Hpc are directly involved in any type of learning and memory consolidation and retrieval (Carter et al., 2006; van Kesteren et al., 2010), the PAG is specifically implicated in aversive learning and prediction error generation, which is crucial for forming long-term pain behavior and nociceptive memory (Roy et al., 2014). If

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pain behavior can be unlearned by altering the aberrant brain connectivity patterns of the PAG in its capacity as a pain-learning brain region, this could potentially stop or even reverse the transition to chronic pain. This led us to investigate whether acupuncture, known to work through the descending pain modulation system (Kong et al., 2010), including the PAG, could be instrumental in normalizing chronic pain brain circuitry.

In this study we examined the relationship between chronic knee osteoarthritis symptoms (measured with the Knee injury and Osteoarthritis Outcome Score (KOOS) pain and sport subscales) and resting state connectivity between PAG–MFC and PAG–Hpc, as both MFC and Hpc are crucial for pain learning, attention and memory. We hypothesized that lower PAG–Hpc connectivity (associated with less attention to pain, anxiety and nociceptive memory) would correlate with better pain and sport scores; in contrast, lower PAG–MFC connectivity (indicating increased attention to pain, low analgesia expectation, higher pain avoidance) would correlate with increased pain and sport scores. We also hypothesized that connectivity in PAG–Hpc and PAG–MFC would be improved by repeated verum acupuncture (compared to sham).

2. Materials and methods

The full details of subject enrollment and inclusion, study design, acupuncture procedures and fMRI acquisition are reported elsewhere (Chen et al., 2014; Spaeth et al., 2013). Here we provide a brief description of the methods and focus on the procedures and analysis details relevant for this study.

2.1. Subjects

Forty-four knee osteoarthritis patients (19 females) were enrolled in the study, of which 30 (13 females, aged 57.5 ± 8.3, mean $\pm$ SD) completed all experimental stages. The Institutional Review Board of the Massachusetts General Hospital approved all study procedures. The subjects provided informed consent at the beginning of the study and were debriefed at the end of the study.

2.2. Experimental design

Subjects in this study had either unilateral or bilateral knee pain, however, they all received acupuncture treatment on either right or left knee (whichever presented with more severe pain). Subsequent treatment and pain assessment only focused on one knee. Subjects were randomized into one of the three groups: 1) verum acupuncture at 6 acupoints, 2) verum acupuncture at 2 acupoints, or 3) sham acupuncture (6 acupoints with Streitberger placebo needles), keeping knee condition (bilateral/unilateral pain predominantly in right/left knee) balanced across groups. After the initial screening, each subject received a total of 6 acupuncture sessions within one month (twice a week during weeks 1–2 and once a week during weeks 3–4). Treatments 1, 3, and 6 were conducted with the patient lying in a 3 Tesla MRI scanner. Treatments 2, 4 and 5 took place in a behavioral testing room.

Verum acupuncture was performed on ST35 and Xiyan points for the low-dose verum groups and additionally at GB34, SP9, GB39 and SP6 for the high-dose group. Both ST35 and Xiyan points are located near the knee. They are typically used in knee pain treatment and have been previously used in osteoarthritis clinical trials (Berman et al., 2004; Cheng, 1987; Scharf et al., 2006; Stux, 1997; Witt et al., 2005). Placebo acupuncture was performed in 6 spots on the lower leg, where no meridians pass through. All subjects received acupuncture treatment on the ipsi-lateral side (i.e., on the painful knee); subjects receiving acupuncture at 6 points had acupuncture performed on both legs, but never uniquely on the contralateral side (Yi et al., 2011).

Each acupuncture session lasted approximately 25 min and was the same for all subjects, regardless of the group assignment. For the purposes of this analysis, subjects in the two verum acupuncture groups were combined, as the two treatment types evoked similar *deqi* sensation, had the same stimulation time and treatment effect, as indicated by KOOS (Spaeth et al., 2013). Compared to verum acupuncture, in which the needle penetrates the skin, sham acupuncture was performed with non-penetrating Streitberger needles (the needle retracts up into the shaft when pressed against the skin). Subjects were blind to the site of needle insertion and to whether the treatment was verum or sham. For the duration of the treatment, subjects agreed not to receive any other medical intervention or medication for their knee osteoarthritis.

Treatment clinical outcomes were measured using the KOOS (Roos et al., 1998), comprising 5 subscales: 1) pain, 2) other symptoms, 3) function in daily living, 4) function in sport and recreation, and 5) knee-related quality of life. Each subscale is measured from 0–100, with a greater score signaling improvement. The KOOS was administered to all patients at baseline (up to one week before treatment 1) and after the final treatment (treatment 6). The scale requires patients to assess their state during the preceding week. Based on our hypotheses and previous results showing significant differences between sham and verum acupuncture (Chen et al., 2014), we only focused on 2 subscales: pain and sport, the latter representing pain ratings during increased physical activity; the other subscales were not analyzed.

2.3. fMRI acquisition and pre-processing

Each subject underwent 3 fMRI scanning sessions. Each scanning session included a 6-minute resting state scan (a), two functional scans during acupuncture (25 min) (b), as well as another 6-minute resting state scan (c), see Fig. 1. We here focus only on the resting state scans (a) before acupuncture treatment during fMRI session 1 and session 3. Resting state session 1 (henceforth 'pre'-acupuncture resting state) was performed before the beginning of repeated acupuncture treatment and within about a week of the measurement of the baseline KOOS (KOOS-pre). Resting state session 3 (henceforth 'post'-acupuncture resting state) was performed approximately 25 days later following 5 acupuncture treatments but before the final (6th) acupuncture treatment. For the resting state scan subjects were required to keep their eyes open. The final KOOS (KOOS-post) was measured on the same day but after the 6th acupuncture treatment was performed, see Fig. 1.

Scanning was performed using a 3-axis gradient head coil in a 3 Tesla Siemens MRI scanner with echo planar imaging (EPI). Structural scans were acquired using a magnetization prepared rapid gradient echo (MPRAGE) sequence with TR = 2200 ms, TE = 9.8 ms, flip angle of 7°, field of view of 230 mm^2, and slice thickness of 1.2 mm. For the resting state analysis, 47 slices were acquired with the following parameters: TR = 3000 ms, TE = 30 ms, flip angle of 85°, the field of view of 216 mm^2, and 3 mm $*$ 3 mm $*$ 3 mm in-plane spatial resolution.

The preprocessing of resting state images was done using SPM 8 software (http://www.fil.ion.ucl.ac.uk/spm) implemented in a MATLAB suite (Mathworks, Inc., Natick, Massachusetts). It included slice time correction, head motion correction, co-registration to subjects' structural images, segmentation, normalization, linear detrending and smoothing (FWHM = 6 mm).

Functional connectivity analysis was carried out with the CONN toolbox (www.nitrc.org/projects/conn) (Whitfield-Gabrieli and Nieto-Castanon, 2012). Timecourses from the components associated with white matter and cerebrospinal fluid (CSF) were regressed out of whole-brain gray matter activity, 12 motion regressors (6 realignment parameters and first derivatives) were used to control for correlations during movement. Data were filtered between 0.008 and 0.09 Hz, global brain signal was not subtracted.

Functional connectivity analysis was performed using an ROI-to-ROI approach. PAG was used as a seed ROI. As PAG mask is not available in