Title: Mechanistic Studies on Video-guided Acupuncture Imagery Treatment of Knee Pain

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I. BACKGROUND AND SIGNIFICANCE

Knee osteoarthritis (OA) is a common disorder among the elderly population in the U.S. that often leads to disability over time. About 27 million adults (more than 50% of arthritis cases in the U.S.) report being diagnosed with OA by their doctor. As life expectancy increases, so does the number of people suffering from joint disease [1].

Despite the high prevalence of OA, treatment of OA is far from satisfactory [1, 2]. Pharmacological treatment of knee OA is often ineffective and has unwanted, sometimes dangerous, side effects [2, 3]. Developing a cost-effective complementary treatment for OA would have a high clinical impact.

Imagery is a commonly used therapeutic method for many disorders such as chronic pain [4-7] and stroke [8-10]. Yet, the underlying mechanism remains unclear. Studies suggest that in addition to directly perceiving one's environment, individuals spend considerable time recollecting and/or imagining experiences [11-13]. A large body of literature suggests that common brain areas are activated during direct and vicarious (observational) experiences [14]. For example, observing others' experience of pain can activate a similar network as is activated when one directly experiences pain [11, 15-22]. Furthermore, investigators have found that imagined painful scenarios from a first-person perspective can be more vivid, less difficult, and less disembodied than scenarios imagined from a third-person perspective [11, 23] and can produce stronger fMRI signal increases at the secondary somatosensory cortex (S2) and insula [23].

As an invasive treatment, acupuncture involves needle insertion and manipulation. Literature suggests that *deqi* (sensations evoked by acupuncture needle manipulation such as soreness, aching, and dull pain) are crucial for treatment effects [24-26]. To the extent that these acupuncture sensations can be elicited by watching a video of acupuncture treatment and imagining the treatment, one would expect that brain activity changes would be produced that overlap with those changes produced by real acupuncture needle manipulation. Indeed, this has been demonstrated by a previous brain imaging study in which investigators found that visualizing images of acupuncture needle stimulation [27] produced overlapping fMRI signal changes in the brain at the anterior insula (AI), middle cingulate cortex (MCC)/dorsal anterior cingulate cortex (dACC), and periaqueductal grey (PAG).

Taken together, these findings provide a solid foundation for VGAIT. Most importantly, applying powerful brain imaging tools to explore the neuroscience of mind-body interaction and then testing its treatment effect in a patient population may elucidate how the mind can alter perception [11] and thereby reshape pain experience to achieve a therapeutic effect.

II. SPECIFIC AIMS

The aim of this proposal is to investigate brain response and connectivity changes evoked by video-guided acupuncture imagery treatment (VGAIT) and verum and sham acupuncture in patient populations to elucidate the underlying brain mechanisms of mind-body interaction, imagery, and acupuncture.

Specific Aim 1: Characterize and compare the brain response evoked by VGAIT, a VGAIT control condition, and real and sham acupuncture in chronic pain patients.

Hypothesis 1.1 VGAIT and real acupuncture will produce overlapping fMRI signal increases in AI, MCC/dACC, and PAG as compared to control and sham acupuncture. Real acupuncture will produce greater fMRI signal increases at primary somatosensory cortex (S1) compared to VGAIT in OA patients**.**

Hypothesis 1.2: Pain intensity ratings of the OA patients will be reduced after about one month of VGAIT and real acupuncture treatment; fMRI signal increases at AI, MCC/dACC, and PAG evoked by treatment will be associated with knee pain intensity reduction after about one month treatment.

Specific Aim 2: Characterize and compare the modulation effects of different treatments on resting state functional connectivity (rsFC) in chronic pain patients.
Hypothesis 2.1: After treatment, the PAG rsFC with ACC/MPFC will be significantly enhanced in the VGAIT and real acupuncture groups, compared to the control condition and sham acupuncture groups.

Hypothesis 2.2: The PAG-ACC/MPFC rsFC increase will be significantly associated with corresponding knee pain intensity reduction.

III. SUBJECT SELECTION

Inclusion/exclusion criteria for patients with knee OA:
125 male and female patients aged 40-75 with a diagnosis of knee osteoarthritis and pain will be recruited for the experiment. A written informed consent form or REDCap eConsent will be obtained in all cases.

Inclusion Criteria:

a) Volunteers 40-75 years of age

b) Meet the Classification Criteria of the American College of Rheumatology for osteoarthritis of the right and/or left knee for at least the past 3 months, as determined by the referring physician

c) Ability to read and understand English; English can be a second language provided that the patient feels he or she can understand all the questions used in the assessment measures.

Exclusion Criteria:

a) Any interventional procedure for knee pain, including corticosteroid injections (within 2 months [28, 29]) to the knee

b) Prior acupuncture treatment for any condition within the past year

c) The intent to undergo surgery during the time of involvement in the study

d) Presence of any illness, medication use, or condition that is judged by the principal investigator to interfere with the trial. For example: skin irritations around the knee such as psoriasis, bleeding disorders or anticoagulant use that would be contraindications for acupuncture, diabetes due to the increased possibility of sensitivity to heat pain, or substance abuse. Use of opiates or other medications is allowable if the participant has been taking a stable dosage of the medication for at least one month. Per the judgment of the principal investigator, we may perform a urine toxicology screen to verify a patient's medication status during Session 1. A positive drug test is not exclusionary unless it contradicts the patient's self-report or indicates the presence of illegal substances.

e) Knee pain due to other causes such as inflammation or malignancy, other pain disorders that may refer pain to the leg, OA of ipsilateral hip, diagnosis of RA

f) Non-ambulatory status. Assistive devices such as walkers/canes are allowable given that patients do not require assistance with said device.

g) History of a chronic disease that, in the investigator's judgment, precludes participation in the study because of a heightened potential for adverse outcome (e.g., asthma or claustrophobia)

h) Presence of any contraindications to fMRI scanning (e.g., cardiac pacemaker, metal implants, fear of closed spaces, pregnancy)

IV. SUBJECT RECRUITMENT

Knee osteoarthritis subjects and healthy controls will be recruited from Research Patient Data Registry (RPDR), a clinical data registry that gathers medical records from many Partners HealthCare hospitals (Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH)). The possible participants identified through RPDR will be contacted through mailed letters or patient gateway letters and targeted announcements. Contingency plans will include advertising through email, web, and bulletin board announcements posted within our hospital network community and pain centers / clinics in Boston area. Our team has extensive experience in recruiting Knee OA patients and if necessary, auxiliary backup methods such as Craigslist, posters, newspapers, and public transportation advertisements will be adopted.

As part of obtaining informed consent, one of the study investigators will review all study procedures to be sure patients are aware of and in agreement with participating in a complete experiment. This will happen during a telephone screening as well as the beginning of their first study visit. Sufficient funds have been budgeted to cover the costs of recruiting and screening additional participants as it is expected that some patients will not pass all the screening criteria described in above.

V. STUDY PROCEDURES

Detailed experimental procedure

Subject recruitment 125 patients with knee OA will be recruited. Please see the *Protection of Human Subjects* and *Other Attachment* sections for more detailed inclusion criteria for the screening and recruitment methods. In addition, we will recruit a cohort of age- and gender-matched non-pain control subjects (n=50); identical imaging and other assessments (when applicable) will be assessed one time only. For both knee OA and control, we will also add the MoCA and blood sample measurements, since both of these measurements will be additional measurements added to parent grant, it will not influence the integrity of the original aims.

Randomization Patients who pass the screening will be randomized into one of the four groups using a centrally generated, variable-sized block design.

Endpoints

Primary outcomes

The primary outcome will be blood oxygen level (BOLD) response (fMRI signal) differences evoked by VGAIT and VGAIT control.

Secondary outcomes

Secondary outcomes will include 1) PAG resting state functional connectivity differences before and after one month of treatment; 2) KOOS Score [30] (we will focus on KOOS pain subscale score based on previous studies [2, 31-33]) and other clinical outcomes (see below for details); and 3) QST [1, 34]. All clinical outcomes will be measured at baseline and after the last treatment.

PAG-ACC/mPFC resting state functional connectivity will be assessed by calculating Pearsons' correlation between the fMRI scan time courses of the PAG and ACC / MPFC using the CONN toolbox *[35]*, while the subject is resting in the fMRI scanner prior to beginning the treatment and again immediately after the treatment. In short, preprocessing of resting state fMRI data will

include co-registration, motion correction, normalization to MNI stereotactic space, and spatial smoothing with an 8 mm Gaussian kernel. Functional connectivity analysis for individual subjects will be carried out using the PAG as a seed. Specifically, the average time course of the PAG will be obtained and correlation analysis will be performed in a voxel-wise way to generate a functional connectivity map for PAG. The resulting correlation coefficient map will be converted into a Fisher-Z map using Fisher's r-to-z transformation to improve the normality, and then will be entered into the group analysis. Group analysis will be performed using CONN toolbox *[35]*. A full factorial module in SPM 12 will be performed to compare the PAG rsFC changes before and after about one month of VGAIT, VGAIT control, real and sham treatments.

Blindness During data acquisition, all study personnel except the administering acupuncturist will be blinded with respect to treatment conditions. Patients will also be blind to acupuncture modality (real or sham) they receive till end of the study, a study investigator will debrief the subject and explain the rational of blindness.

Experimental procedure

Session 1 will be a behavioral session to train subjects for QST responses, and reduce anticipatory anxiety to treatments. Subjects will complete a set of clinical and psychometric measurements. Recently, EEG has been applied to investigate both acupuncture *[36]* and chronic pain *[37]*. We will thus collect approximately 12 minutes of resting state EEG for exploratory analyses to test 1) if different treatment can modulate the power spectrum of different EEG frequency bands and 2) if power spectrum of different EEG frequency bands at baseline can be used to predict treatment response.

Then, based on the randomization, they will be introduced to different treatments. Those who are randomized to the real acupuncture and VGAIT groups will receive real acupuncture treatment (about 5 minutes); the procedure will be videotaped for those in the VGAIT group. For those in the sham acupuncture group, sham acupuncture will be introduced. For those in the VGAIT control touching group, we will explain the situation and videotape the touching exposure process. For those in the VGAIT and VGAIT control groups, we will explain the potential underlying mechanism of how imagery treatment works and inform them that the more vividly they can imagine treatment based on the video, the better the result will be. Subjects will then be introduced to the MGH Acupuncture Sensation Scale (MASS) to report their sensations as described below**.**

Blood marker test Using a method described in a previous study [38], peripheral blood samples for circulating markers will be collected by venipuncture in EDTA tubes. The samples (about 10 mL) will be immediately placed on ice and centrifuged for acquisition of plasma within one hour. The aliquots will then be stored at −80 °C for subsequent batch testing at baseline, week 4, week 8, and the 3 follow-up sessions. We will examine inflammatory mediators such as interleukins (ILs including IL-1alph and beta , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, and IL-10), IFN-γ, and tumor necrosis factor (TNF) via multiplex immunoassays using Luminex, as well as highly sensitive C-reactive protein (hsCRP), TNF-α programmed death 1 (PD-1), prostaglandin E_2, and BDNF via Enzyme Linked Immuno Assay (ELISA). All tests will be administered at the Clinical Research Center at the Massachusetts General Hospital that will provide all proposed test.

Clinical and psychometric measurements All clinical assessments will be completed by patients during their first visit (session 1) and during their last visit (session 8). Question 6 (pain rating now, 0-10 scale) of the BPI and ERS will be repeated at the beginning and end of all fMRI scan sessions. The MASS will be administered after all treatments. The complete KOOS and BPI will be administered during patients' first and final study visits.

Knee Injury and Osteoarthritis Outcomes Score (KOOS): The KOOS is a 35-item self-administered survey of pain and function in knee OA patients [30]. It contains the WOMAC

items (Western Ontario and McMaster Universities Osteoarthritis Index) and additional items for pain and functional ratings. It may be more sensitive to subtle improvements in function than the WOMAC [39]. KOOS is comprised of 5 subscales: 1) pain, 2) other symptoms, 3) function in daily living (ADL), 4) function in sport and recreation, and 5) knee-related quality of life (QOL). Each subscale allows for calculation of a normalized score, with 0 denoting the most extreme symptoms/pain and 100 denoting no symptoms/pain [30]. Based on previous studies [2, 31-33], we will focus on the KOOS pain subscale.

Brief Pain Inventory (BPI): The BPI is a 15-item questionnaire rating pain location, intensity, relief, and quality, as well as pain-related quality of life, and it has been validated in many pain studies [40, 41].

Beck Depression Inventory (BDI): The 21-item BDI has shown good sensitivity and specificity for major depression in chronic pain patients [42, 43]. BDI scores greater than 20 will be considered high for depression symptoms [42].

MGH Acupuncture Sensation Scale (MASS): The MASS includes 12 descriptors of common acupuncture sensations: soreness, aching, deep pressure, heaviness, fullness/distension, tingling, numbness, sharp pain, dull pain, warmth, cold, and throbbing with one supplementary row at the end of the descriptors for subjects to describe their perceptions in their own words [25]. We have developed an EPrime script that allows us to collect subject MASS ratings while they are in the scanner, using a projector and a button response system.

Betts' Questionnaire upon Mental Imagery (BQMI): We will use the BQMI to measure the imagery vividness of VGAIT in this study. The BQMI consists of 35 items. Each item of image vividness is rated on a 7-point scale, and the procedure is undertaken with the eyes open.

Expectations for Relief Scale (ERS): The ERS is a 0-10 scale used to measure the expectation of post-acupuncture pain relief. During every fMRI scan session, after each verum or placebo acupuncture treatment, subjects will be asked to use the scale to rate how much pain relief they expect from this particular treatment, with 0 indicating a very negative expectation of "does not work at all" and 10 indicating a very positive expectation of "complete pain relief." Studies have shown that expectation can significantly influence an individual's perception of pain relief [44-50].

State-Trait Anxiety Inventory (STAI): The STAI consists of two 20-item self-report inventories. It is a rapid but detailed assessment that distinguishes between basal (part one inventory) and reactive (part two inventory) anxiety [51]. Scores range from 20 to 80 with higher scores indicating a greater level of anxiety. Some studies suggest that subjects with high initial anxiety scores tend to experience more pain relief after acupuncture treatment than those with low anxiety scores [52, 53].

Sessions 2-7 are acupuncture treatment visits. Session 2 (treatment 1) will be applied in the fMRI scanner. Based on previous studies from other groups [2, 54, 55] and our group [31, 32, 56, 57], we decided to administer treatment six times in about one month (approximately two times per week for the first two weeks and one time per week for the last two weeks). While we prefer study sessions to occur at these intervals, scheduling adjustments can be made without affecting the integrity of the research. The rationale for this is that the effects of acupuncture have been shown to last up to six months following the intervention, so slight adjustments to the preferred treatment plan are not consequential to treatment effects.

All brain imaging will be performed with a 3-axis gradient head coil in a 3 Tesla Siemens MRI System equipped for echo planar imaging. A high-resolution 3D MPRAGE sequence will be collected for anatomic localization of significant signal changes. Functional MRI images will be acquired using a gradient echo T2*- weighted pulse sequence (TR/TE = 2000/30ms, flip angle =

90˚, FOV = 192x192 mm, 48 AC-PC aligned slices, slice thickness = 3.0 mm with 0.6 mm inter-slice gap, 90 image volumes per slice, matrix = 96x96). fMRI scans will include one resting state scan (8 minutes) during which subjects will be told to open their eyes and two ten-minute scans of different treatments, which is identical to our previous study.

All participants will be asked to fill out the MGH Acupuncture Sensation Scale (MASS) following each treatment. Additionally, participants randomized to the video conditions will fill out the Vividness Scale. The Vividness scale will use a 0-10 vividness scale to measure imagery vividness during the fMRI scans. The scale ranges from Not Vivid/Unclear (0) to Vivid/Clear (10).

Session 8 will involve a resting state MRI scan. In addition, subjects will complete the clinical and psychometric measurements used during session 1 and undergo QST testing. Subjects will complete the Final Questionnaire during this session and EEG data will be collected.

Procedures for video guided acupuncture imagery treatment and control condition VGAIT and control conditions will last about 25 minutes; the time is the same as real acupuncture (see the following for details). The same licensed acupuncturist will carry out the VGAIT and control conditions.

Procedures for acupuncture administration Similar to our previous studies [31, 32, 56, 57], acupuncture procedures will last approximately 30 minutes in total and will be carried out by a licensed acupuncturist on the side with the most severe symptoms or the side as chosen by subjects to need more treatment.

Verum acupuncture procedures Verum acupuncture will be applied on ST35, Xi Yian (extra point), GB34, SP9, GB39, and SP6 based on literature [2, 32, 54, 56-60]. After insertion and obtainment of *deqi* sensation, needles will be manipulated in the order of GB34, SP9, ST35, Xi yuan (extra point), GB39, and SP6.

Placebo (sham) acupuncture procedures Placebo acupuncture will be applied at six sham points using sham acupuncture needles [24, 49, 61-63]. S*ham point 1* is located 1 cun posterior to the superior 1/3 of K9 and K10, *sham 2* is located 1 cun posterior to K8, *sham 3* is located at midpoint of sham 1 and 2, *sham point 4* is located 1.5 cun anterior and inferior to GB34, and *sham points 5-6* are located 1.5 cun and 3 cun inferior to sham point 2, sham points 7-8 are located 1.5 cun and 3 cun inferior to sham point 4, respectively. All sham points are located on the lower leg where there is no meridian passing through.

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