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Characterizing the analgesic effects of real and imagined acupuncture using functional and structure MRI

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Abstract

Acupuncture and imagery interventions for pain management have a long history. The present study comparatively investigated whether acupuncture and video-guided acupuncture imagery treatment (VGAIT, watching a video of acupuncture on the participant's own body while imagining it being applied) could modulate brain regional connectivity to produce analgesic effects. The study also examined whether pre-intervention brain functional and structural features could be used to predict the magnitude of analgesic effects. Twenty-four healthy participants were recruited and received four different interventions (real acupuncture, sham acupuncture, VGAIT, and VGAIT control) in random order using a cross-over design. Pain thresholds and magnetic resonance imaging (MRI) data were collected before and after each intervention. We first compared the modulatory effects of real acupuncture and VGAIT on intra- and inter-regional intrinsic brain connectivity and found that real acupuncture decreased regional homogeneity (ReHo) and functional connectivity (FC) in sensorimotor areas, whereas VGAIT increased ReHo in basal ganglia (BG) (i.e., putamen) and FC between the BG subcortical network and default mode network. The altered ReHo and FC were associated with changes in pain threshold after real acupuncture and VGAIT, respectively. A multimodality fusion approach with pre-intervention ReHo and grey matter volume (GMV) as features was used to explore the brain profiles underlying individual variability of pain threshold changes by real acupuncture and VGAIT. Variability in acupuncture responses was associated with ReHo and GMV in BG, whereas VGAIT responses were associated with ReHo and GMV in the anterior insula. These results suggest that through different pathways both real acupuncture and VGAIT can modulate brain systems to produce analgesic effects.

Key words: Intra-regional connectivity, Inter-regional connectivity, acupuncture, video-guided acupuncture imagery treatment, gray matter volume.

Highlights

Acupuncture decreased brain connectivity in sensorimotor areas to produce analgesic effects.

Imagery acupuncture increased basal ganglia connectivity to produce analgesic effects.

Functional and structural brain metrics jointly predict participant's analgesic effect.

1. Introduction

Despite the universality of acute pain and the high prevalence of chronic pain, current treatment regimens for pain are ineffective for a significant number of individuals. Few nonopioid and nonaddictive pain medications have been developed to treat pain over the past five decades (Mao, 2012). As a traditional therapeutic approach that stimulates certain points of the body with needles, acupuncture has been found to induce the release of endogenous opioids (Dougherty et al., 2008; Han, 2003; Pomeranz, 1996) and relieve pain by modulating brain regions and networks associated with pain perception and modulation (Dhond et al., 2008; Egorova et al., 2015; Fang et al., 2009; Kong et al., 2007; Tu et al., 2019a; Yu et al., 2020).

The use of imagery is one of the oldest medical practices for treating illness, including chronic pain (Berna et al., 2012, 2011; Giacobbi et al., 2015; MacIver et al., 2008) and stroke (Faralli et al., 2013; Villiger et al., 2013). In addition, studies have shown that the experience of acupuncture needle stimulation and the visualization of acupuncture needle stimulation can provoke overlapping activations in brain regions such as the anterior insula (AI), middle cingulate cortex (MCC), dorsal anterior cingulate cortex (dACC), and periaqueductal grey (PAG) (Cheng et al., 2007). In a previous study, we found that video-guided acupuncture imagery treatment (VGAIT), which involves watching a video of acupuncture previously administered on the participant's own body while imagining it being concurrently applied, can increase pain threshold and modulate key regions in the descending pain modulatory system (e.g, rostral anterior cingulate cortex, rACC) (Cao et al., 2019). Jung et al. (2015) found that both genuine-and pseudo-stimulation resulted in brain activations in the insula, anterior cingulate cortex, secondary somatosensory cortex, superior parietal cortex. In a recent published preliminary study, we found that 4-week VGAIT can produce a similar effect as 4-week real acupuncture in patients with chronic low back pain (Cao et al., 2020).

4

Nevertheless, there are critical gaps in our understanding of VGAIT's underlying neural mechanism. First, the study by (Cao et al., 2019) investigated functional magnetic resonance imaging (fMRI) signal change during the application of VGAIT (i.e., online effects) and acupuncture. However, the means by which VGAIT modulates brain activity and connectivity (i.e., offline effects) and their association with changes in participants' pain thresholds remains unknown. Second, individual variability associated with acupuncture and VGAIT responses is not well understood. Elucidating the underlying mechanisms associated with this variability in treatment response would seem important to the development of more effective interventions. A pertinent question is whether measures of brain structure, which may represent the participant's inherent response to the intervention, and functional activity, which may capture the participant's brain state prior to the intervention, can provide insight into an individual's potential responsiveness to the intervention.

Recent developments in human neuroimaging enable us to study the offline effects of VGAIT, as well as characterize individual differences in intervention response. For example, resting-state fMRI can reveal changes in brain activity and connectivity following VGAIT (Bai et al., 2009; Chen et al., 2018; Dhond et al., 2008; Tu et al., 2019a). In addition, an increasing number of studies have used multimodal data to investigate brain mechanisms that underlie pain (Dougherty et al., 2008; Tracey and Bushnell, 2009; Tu et al., 2016a, 2016b). However, these studies typically analyze each modality independently and not the interactions between them. State-of-the-art multimodality fusion approach (Qi et al., 2018; Sui et al., 2015, 2012), which combines fMRI and structural magnetic resonance imaging (sMRI), takes advantage of cross-information within the two MRI modalities. This can reveal important joint contributions to the participant's brain state (i.e., functional activity prior to an intervention) and susceptibility (i.e., brain structural properties) for intervention responsiveness. This provides a perspective that may only partially be detected when examining a single modality.

5

In the present study, we analyzed behavioral (i.e., changes in pain threshold), fMRI and sMRI data from 24 participants who received four different interventions (i.e., real acupuncture, sham acupuncture, VGAIT, and VGAIT control) in random order using a cross-over design. We first investigated the modulatory effects of acupuncture and VGAIT on intra- and inter-regional brain connectivity between the resting-state fMRI before and after each intervention. We then combined participant's state (as reflected by fMRI before intervention) and trait (as reflected by sMRI) brain metrics to investigate responsiveness to acupuncture and VGAIT using a multimodality fusion approach (multi-set canonical correlation analysis, MCCA) (Fu et al., 2019; Sui et al., 2015). MCCA is a promising method that can be used to explore co-variation in multimodal neuroimaging data. Specifically, it is a data-driven method that decomposes features of each modality into associated components and their corresponding canonical variants (Sui et al., 2012). It aims to identify co-varying brain patterns among two or more modalities by maximizing the inter-modality correlations between canonical variants (Sui et al., 2015). In the present study, the fMRI-sMRI joint information identified by MCCA was correlated with participant's changes in pain threshold to find a potential multimodal predictor of intervention responsiveness.

2. Methods

Full details of the study have been previously reported (Cao et al., 2019), in a study that investigated fMRI signal changes evoked by real and imagined acupuncture. The present work is focused on the modulation effect of real and imagined acupuncture (as compared to sham acupuncture and imagined acupuncture control) on resting-state functional connectivity before and after intervention and whether the intervention response (analgesia) can be predicted by combining information about pre-intervention resting-state functional connectivity and brain structure.

2.1 Participants

Twenty-seven healthy, right-handed, acupuncture-naïve individuals were recruited for the study. The study was approved by the Partners Human Research Committee (IRB) of Massachusetts General Hospital. All participants gave written informed consent prior to participating in the study.

2.2 Study procedure

In brief, the study included five sessions: an initial training and familiarity session (Session 1), and four intervention sessions (Session 2-5). Each intervention session consisted of pain threshold assessments and fMRI recording, during which the participants received one of the four interventions: a) real acupuncture, b) sham acupuncture, c) VGAIT, or d) VGAIT control condition. Intervention sessions were applied in a random order and separated by at least 7 days to avoid residual effects of the previous session (Figure 1). Details of the experimental design have been previously described (Cao et al., 2019) and are provided in Supplementary Material 1.
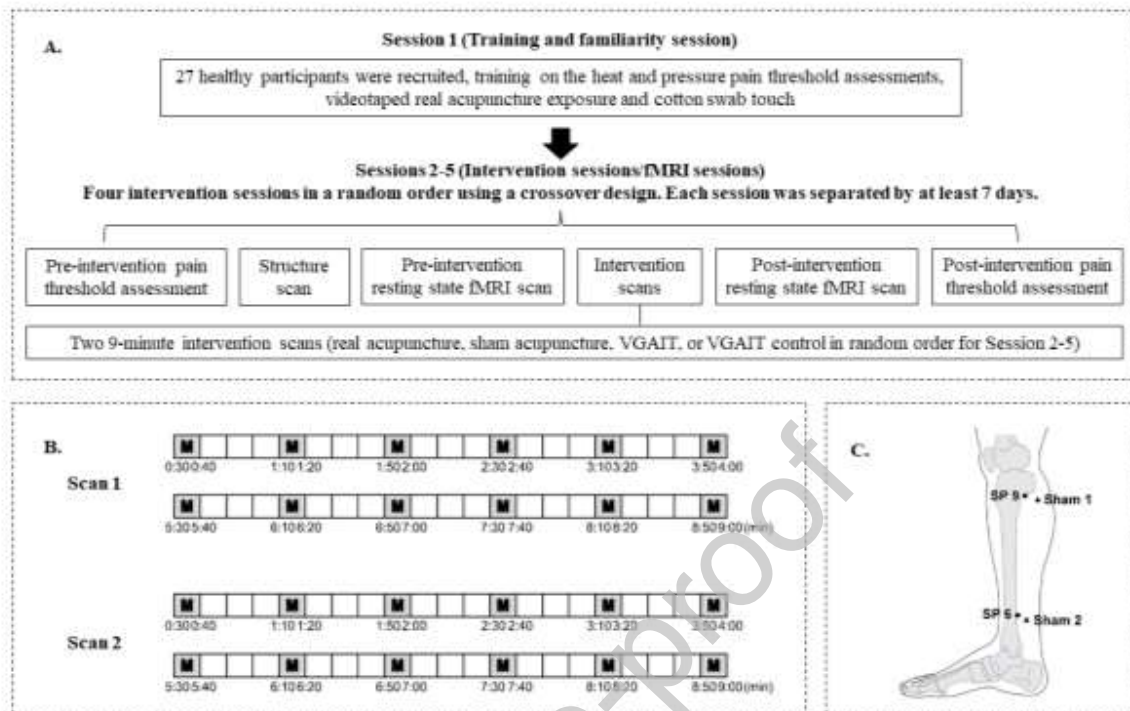
Figure 1. Flowchart of the study procedure and acupuncture points. A) Flowchart of the study procedure that included four different interventions administered on four separate sessions. B) Two 9-minute intervention scans (M represents needle manipulation or video performance). C) Location of acupoints [dot] and sham points [triangle]. Abbreviations: fMRI, functional magnetic resonance imaging; VGAIT, video-guided acupuncture imagery treatment; SP 6, Sanyinjiao (Spleen 6); SP 9, Yinlingquan (Spleen 9).

2.2.1 Session 1: Training and familiarity session

Participants were trained on the heat and pressure pain threshold assessments using Quantitative Sensory

Testing (QST) and learned to minimize anticipatory anxiety to the interventions. The potential mechanism

underlying guided imagery treatment for pain relief was explained, and participants were instructed to

vividly imagine the intervention while watching the video. At the end of the session, participants received

5-minute real acupuncture exposure, which was videotaped for the VGAIT intervention. A cotton swab

was used to touch non-acupoints (sham points), which was videotaped for the VGAIT control

intervention (Figure 1).

2.2.2 Sessions 2-5: Intervention sessions

Real and sham acupuncture procedures were carried out by a licensed acupuncturist; all intervention lasted about 20 minutes. Specifically, for the real acupuncture intervention, right Sanyinjiao (Spleen 6, SP 6) and Yinlingquan (Spleen 9, SP 9) were selected (Figure 1C, dots). Needles were rotated at one point and then another in 10-second rotations with 30-second breaks (Figure 1B). The starting acupoint was randomized across participants but remained the same between the two 9-minute fMRI scans. The leg position and manipulating parameters were consistent for each participant. In the sham acupuncture intervention, well-validated Streitberger needles (Kong et al., 2006; Streitberger and Kleinhenz, 1998; White et al., 2003) were applied at two sham points (Figure 1B, triangles) and participants were asked whether they could feel the needle. During the sham acupuncture intervention, the leg position and manipulating parameters were identical to real acupuncture.

In the VGAIT and VGAIT control sessions, participants were first provided text instruction for the imagery intervention, then VGAIT/VGAIT control was performed. A full detailed description of the interventions can be found in Supplementary Material 2.

2.2.3 Pain threshold measurements

Two pain modalities (heat and pressure pain thresholds) were assessed with the brief QST before and after each intervention in a quiet room outside the scanner. We chose two body sites (local and distal) for the pain threshold measurement because local and distal pain threshold may represent segmental analgesic effects and suprasegmental analgesic effects, respectively (Coronado et al., 2011). A detailed description of the QST procedure can be found in our previous publications (Cao et al., 2019; Tu et al., 2019b) and Supplementary Material 1.

2.3 MRI acquisition

Two resting-state fMRI scans were performed before and after the interventions. All fMRI data were acquired using a 32-channel head coil in a 3 Tesla Siemens MRI System equipped for echo-planar imaging. Blood-oxygen-level dependent (BOLD) images were collected with 44 slices (3 mm-thick), 3000 ms repetition time (TR), 30 ms echo time, 90 degree flip angle, 2.6×2.6 mm in-plane resolution, and a total of 164 volumes. During the resting-state fMRI, participants were asked to keep their eyes open and to blink normally while looking at a darkened screen and not to think about anything in particular for approximately 8 minutes. A high-resolution structural data (3-dimensional magnetization-prepared rapid acquisition with gradient echo [3D MPRAGE] sequence) was acquired before functional imaging.

2.4 fMRI preprocessing

Resting state fMRI data were preprocessed using CONN toolbox version 17f (https://www.nitrc.org/projects/conn). The first five scans were removed for signal equilibrium and participants' adaptation to the scanner's noise. Preprocessing steps included a standard pipeline (slice-timing correction, realignment, unwarping, spatial normalization, and smoothing with a 5 mm full-width at half-maximum [FWHM] Gaussian kernel). Nuisance regression using white matter and cerebrospinal fluid signals and linear and polynomial trends of head motion were performed (Power et al., 2014). ART (http://www.nitrc.org/projects/artifact_detect/) was also applied to detect motion during the resting-state fMRI scans. Time points in participants' images were marked as outliers if the global signal exceeded three standard deviations from the mean or if scan-to-scan motion deviation exceeded 0.5 mm.

Structural MRI data were analyzed using the Computational Anatomy Toolbox (CAT12, http://www.neuro.uni-jena.de/cat/) in SPM12. Data preprocessing included bias-field and noise removal, skull stripping, segmentation into gray and white matter, and normalization to Montreal Neurological Institute (MNI) space. The quality of images was assessed with the built-in image-quality rating and manually checked by the authors. Gray matter was spatially smoothed using the same 5 mm FWHM Gaussian smoothing kernel as was used in the analysis of fMRI data.

2.5 Data analysis

2.5.1 Behavioral data analysis

Behavioral data analysis has been detailed in our previous publication (Cao et al., 2019) and is provided

in Supplementary Material 3. Briefly, for each of the pain threshold measures (i.e., heat pain on leg, heat

pain on arm, pressure pain on leg, and pressure pain on thumbnail), one-way repeated measures analysis

of variance (ANOVA) was conducted on the changes of pain threshold after interventions. When the main

effect was significant, post-hoc pairwise t-test was performed, and p values were Bonferroni corrected.

2.5.2 Intra-regional connectivity analysis

To measure the intra-regional synchronization before and after each intervention, we used regional

homogeneity (ReHo) (Zang et al., 2004), which has been widely used to detect regional synchronization

in both healthy and clinical populations. The implementation of ReHo was based on the REST software

(http://www.restfmri.net/forum/REST). Kendall's coefficient of concordance (KCC) was used to measure

the similarity of time series between a given voxel and its 26 nearest neighboring voxels, resulting in a

voxel-wise ReHo map for each participant (Zang et al., 2004). We performed ReHo analysis on the

unsmoothed resting-state fMRI data and smoothed the resulting whole-brain ReHo maps with 5-mm

FWHM Gaussian kernel. The smoothed ReHo maps were used for the following statistical analyses.

We first investigated whether there were any significant differences in baseline intra-regional brain

connectivity across the four intervention sessions by applying a one-way repeated measures ANOVA on

the pre-intervention ReHo maps. Then we studied the changes of intra-regional brain connectivity after

interventions. Pairwise t-tests were conducted to compare whole-brain ReHo maps between 'Post-Pre real

acupuncture' and 'Post-Pre sham acupuncture,' as well as between 'Post-Pre VGAIT' and 'Post-Pre

VGAIT control,' to statistically assess the changes in ReHo values after the acupuncture and VGAIT

11

interventions, respectively. Statistically significant effects were determined at a voxel-wise level of $p < 0.001$ and false-discovery-rate (FDR) cluster-corrected threshold $p_{FDR} < 0.05$.

We then performed correlation analysis by correlating the mean of ReHo value changes within clusters that were significantly modulated by the interventions (i.e., real acupuncture and VGAIT) with the changes in pain thresholds. To reduce multiple comparisons, we selected one of four pain threshold measures which was most modulated by real acupuncture (i.e., heat pain threshold on leg) and VGAIT (i.e., pressure pain threshold on leg), respectively, for the correlation analysis (see Results for details).

2.5.3 Inter-regional connectivity analysis

For the inter-regional connectivity analysis, resting-state fMRI data were parcellated into regions of interests (ROIs) and networks according to Power's functional atlas (Power et al., 2011). Of 264 ROIs defined in the atlas, we selected 191 ROIs and 6 networks, including the sensorimotor network (SMN) (Dhond et al., 2008; Tu et al., 2019a), default mode network (DMN) (Buckner et al., 2008; Tu et al., 2019a), basal ganglia subcortical network (SCN) (Bingel et al., 2006), frontal-parietal/cingulo-opercular network (FPN/CON) (Mao et al., 2014), salience network (SN) (Borsook et al., 2013), and visual network (VSN) (Napadow et al., 2010; Shen et al., 2019), which are closely associated with pain perception. Regional mean time series were obtained for each participant by averaging the fMRI time series over all voxels in each of the 191 regions. Functional connectivity (FC) for each participant was measured by the Fisher z-transformed pairwise Pearson correlation coefficient between all possible ROI pairs. A symmetric connectivity matrix was constructed to represent these connections. In the present study, we focused on the changes of FC within and between 6 networks other than individual ROIs. The within network FC was obtained by averaging all FCs of ROIs in one network connecting to other ROIs in the same network. The between network FC was obtained by averaging all FCs of ROIs in one network connecting to other ROIs in the other 5 networks.

12

Similar to the intra-regional statistical analyses, we first applied a one-way repeated measures ANOVA to the pre-intervention FCs to examine whether there was any significant difference in baseline inter-regional brain connectivity. Next, we calculated change scores for each intervention, i.e., Post-Pre real acupuncture, Post-Pre sham acupuncture, Post-Pre VGAIT, and 'Post-Pre VGAIT control. The change scores were then compared between real acupuncture and sham acupuncture and between VGAIT and VGAIT control using pairwise t-tests to statistically assess the changes in FC after acupuncture and VGAIT interventions, respectively. The FDR correction was performed on the p values in the lower triangle (including the diagonal values) of the inter-regional connectivity matrix (see Figure 5B for details). Brain networks significantly modulated by real acupuncture and VGAIT were then correlated with changes in pain threshold.

2.5.4 MCCA fusion analysis

We used whole-brain voxel-wise pre-intervention ReHo maps (fMRI) and segmented grey matter volume (GMV) maps (sMRI) as fusion inputs. As shown in Figure 2, MCCA jointly decomposes two datasets into mixing coefficients (matrices A_1 and A_2) and components (C_1 and C_2), by which modality correlation between A_1 and A_2 is maximized. Consequently, the corresponding columns of A_1 and A_2, also called canonical variants (CVs), are linked between modalities and can be used to evaluate the relationship with pain threshold changes. Their associated spatial maps further demonstrate multimodal integrations that vary similarly across all participants (Sui et al., 2015).

Fusion analysis was performed separately for real acupuncture (input: ReHo maps before real acupuncture treatment and GMV maps) and VGAIT (input: ReHo maps before VGAIT and GMV maps). We chose 8 as the number of CVs based on the minimum description length (Li et al., 2007) and more than 99% of the variance was retained for both modalities. We then correlated the pairs of CVs (one pair contains a CV for ReHo and a CV for GMV) with pain threshold changes. We did not correct for multiple
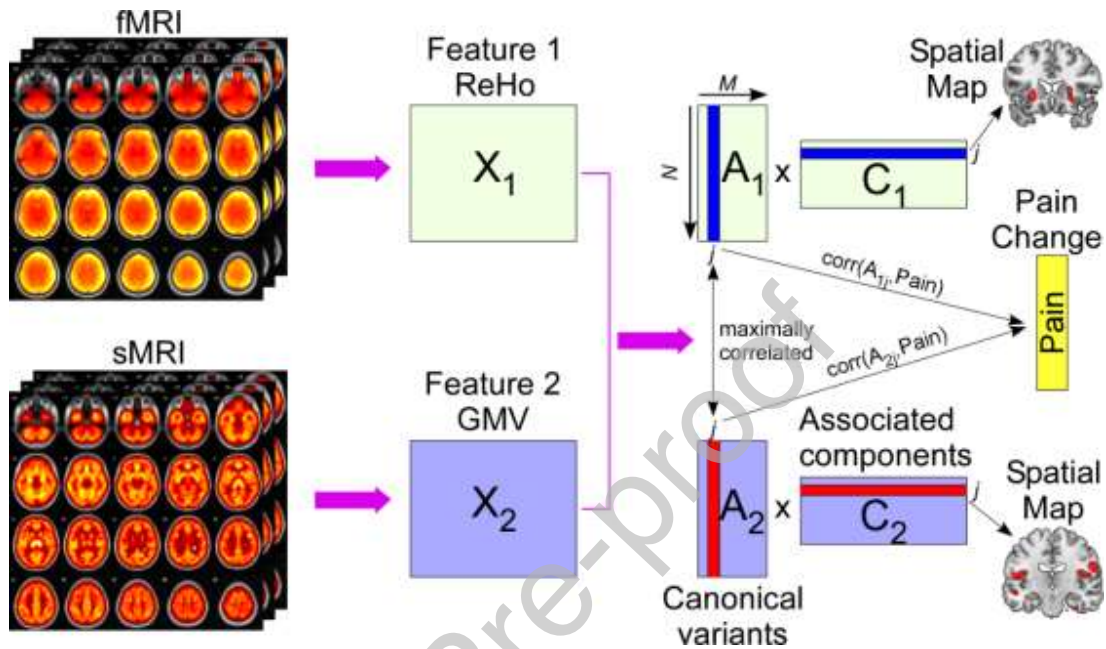
13

Figure 2. Flowchart of the multi-set canonical correlation analysis (MCCA) on fMRI and sMRI.
Step 1: Extract ReHo maps from fMRI data and grey matter volume (GMV) maps from MRI data. Step 2: Run MCCA on these features, which will separate each feature into canonical variants (A_1 and A_2) and associated components (C_1 and C_2). The canonical variants will have high correlations between modalities. Step 3: Correlate the pair of canonical variants A_{1j} and A_{2j} with pain threshold changes.

3. Results

3.1 Behavioral results

Twenty-four participants (age 25.2 ± 0.8; 16 females) completed the study and were included in the analyses. We found significant changes in heat and pressure pain threshold following the interventions (Figure 3). Real acupuncture increased participants' heat and pressure pain thresholds significantly more than sham acupuncture. VGAIT increased participants' pressure, but not heat, pain thresholds more than VGAIT control. Detailed demographic, neuropsychologic, and pain threshold results can be found in Supplementary Material 3 and our previous publication (Cao et al., 2019).
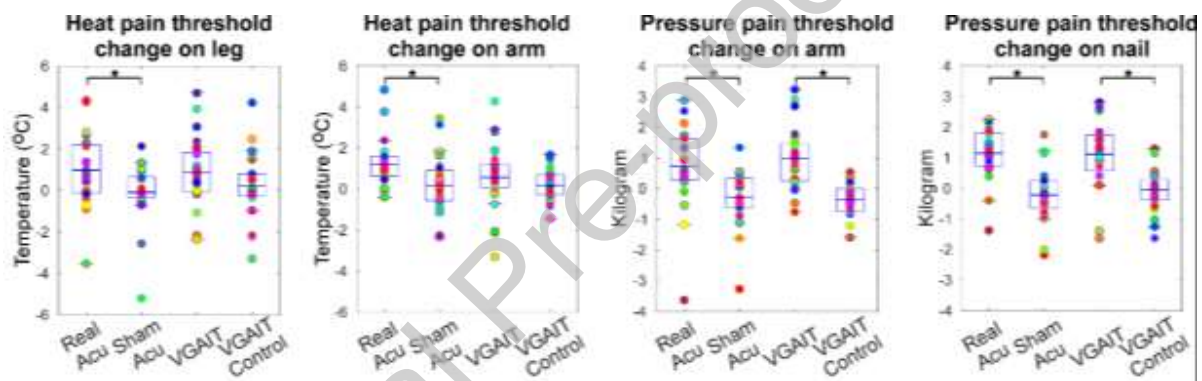

Figure 3. Heat and pressure pain threshold changes from pre- to post- intervention (post minus pre) for the four intervention groups. Boxplots of heat and pressure pain threshold changes after different interventions. Each colored circle represents an individual's pain threshold change. The blue box represents the 25th and 75th percentiles, and the blue line represents the mean of pain threshold changes across 24 participants. *p < 0.05. Abbreviations: Real Acu, real acupuncture treatment; Sham Acu, sham acupuncture treatment; VGAIT, video-guided acupuncture imagery treatment.

3.2 Real acupuncture and VGAIT modulate intra-regional connectivity

We did not find any significant differences across pre-intervention ReHo maps. In contrast, as shown in Figure 4, compared to sham acupuncture, real acupuncture significantly decreased ReHo values in the middle cingulate cortex (MCC), bilateral precentral gyrus (PreCG), and left postcentral gyrus (PoCG) (Table 1). In particular, the exploratory association analysis showed that the changes of ReHo in left PoCG were correlated with changes in heat pain threshold ($r = -0.53$, $p = 0.01$) (Figure 4A).

15

Compared to VGAIT control, VGAIT significantly increased ReHo values in the left putamen (Table 1). The exploratory association analysis showed that ReHo changes in the left putamen were correlated with changes in pressure pain threshold ($r = 0.42$, $p = 0.05$) (Figure 4B). We did not observe any significant clusters when comparing real acupuncture and VGAIT (i.e., 'Post-Pre real acupuncture' vs. 'Post-Pre VGAIT'). Changes in ReHo after the four interventions are shown in Supplementary Figure 2.
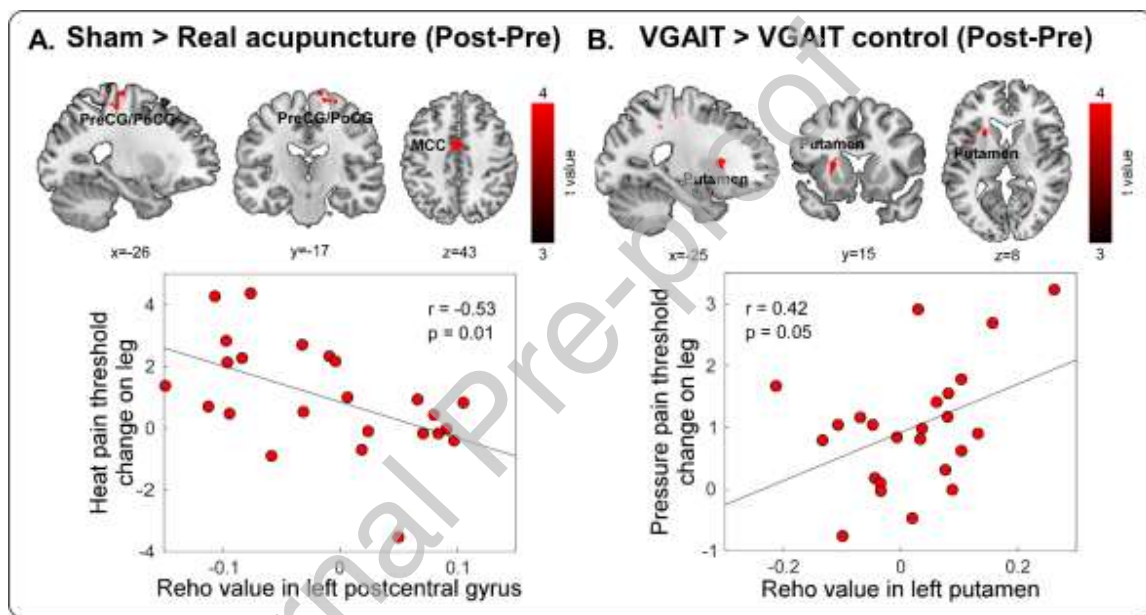

Figure 4. Real acupuncture and VGAIT modulate intra-regional connectivity. A) Compared to sham acupuncture, real acupuncture significantly decreased ReHo values in the middle cingulate cortex (MCC), bilateral precentral gyrus (PreCG), and left postcentral gyrus (PoCG). The changes in ReHo in the left PoCG were correlated with changes in heat pain threshold ($r = -0.53$, $p = 0.01$). B) Compared to VGAIT control, VGAIT significantly increased ReHo values in the left putamen. The ReHo changes in the left putamen were correlated with changes in pressure pain threshold ($r = 0.42$, $p = 0.05$).

16

Table 1. Comparison of intra-regional connectivity in sham minus real acupuncture and VGAIT minus VGAIT control.

Comparisons	Brain Regions	Cluster *p* (FDR-corrected)	Cluster Size	Peak T	MNI coordinates x	y	z
Sham Acu > Real Acu	Right PreCG/PoCG	*p* = 0.001	84	6.42	10	-18	78
	MCC	*p* < 0.001	208	6.10	-2	-4	44
	Left PreCG	*p* < 0.001	180	5.28	-28	-20	68
	Left PoCG	*p* < 0.001	159	4.54	-42	-36	60
VGAIT > VGAIT control	Left Putamen	*p* = 0.029	53	5.78	-24	14	8

Notes: Statistically significant effects were determined at a voxel-wise level of p < 0.001 and false-discovery-rate cluster-corrected threshold of p_{FDR} < 0.05. Abbreviations: Real Acu, real acupuncture; Sham Acu, sham acupuncture; VGAIT, video-guided acupuncture imagery treatment; PreCG, precentral gyrus; SFG, superior frontal gyrus; MCC, middle cingulate cortex; SMA, supplementary motor area; PoCG, postcentral gyrus.

3.3 Real acupuncture and VGAIT modulate inter-regional connectivity

The fMRI data were divided into six networks (Figure 5A). Pre-intervention within- and between-network FCs did not significantly differ. In contrast, as shown in Figure 5B, real acupuncture significantly decreased FC within the SMN, compared to sham acupuncture. Exploratory association analysis showed that the changes of SMN FC were correlated with changes in heat pain threshold on the leg (r = -0.33, p = 0.05).

Compared to VGAIT control, VGAIT significantly increased FC between the SCN and DMN. Exploratory association analysis showed the changes of DMN-SCN FC were correlated with changes in pressure pain threshold on the leg (r = 0.41, p = 0.04). Direct comparison between real acupuncture and VGAIT (i.e., Post-Pre real acupuncture vs. Post-Pre VGAIT) did not produce significant differences at the threshold we set.
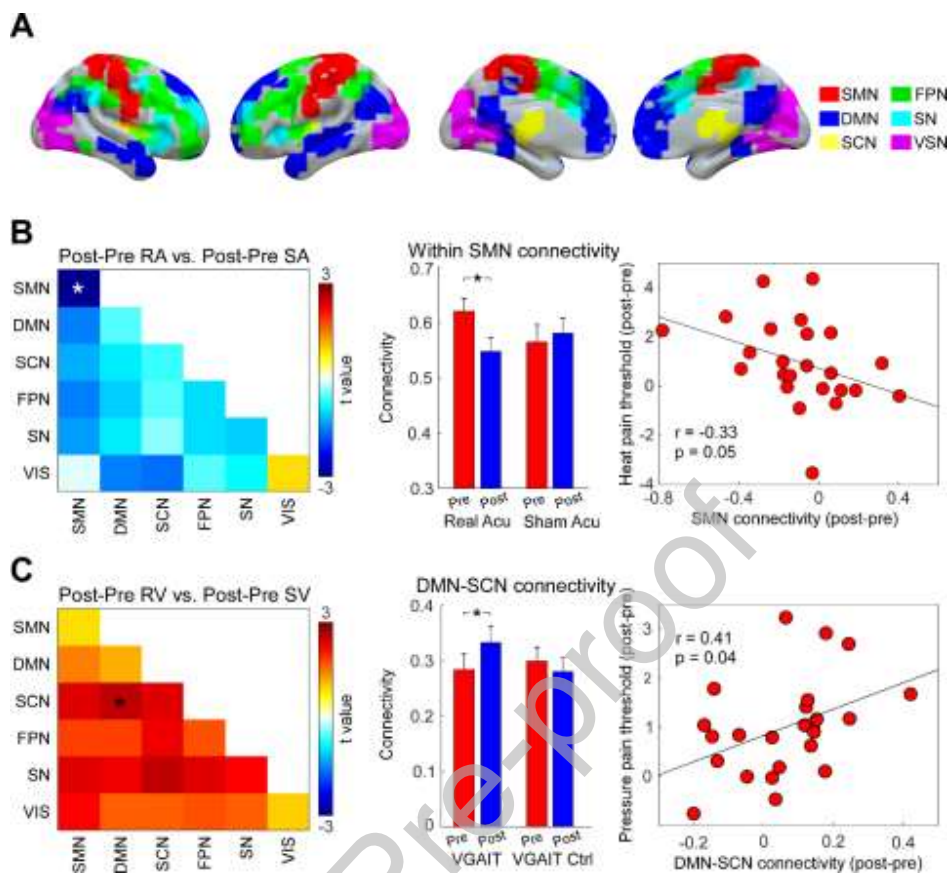
Figure 5. Real acupuncture and VGAIT modulate inter-regional brain connectivity. A) The fMRI data were parcellated into six networks, including the sensorimotor network (SMN), default mode network (DMN), subcortical network (SCN), frontoparietal network (FPN), salience network (SN), and visual network (VSN). B) Compared to sham acupuncture (Sham Acu), real acupuncture (Real Acu) significantly reduced connectivity within SMN. Changes in SMN connectivity were correlated with the changes in heat pain threshold. C) Compared to VGAIT control (VGAIT Ctrl), VGAIT significantly increased FC between SCN and DMN, and the changes of DMN-SCN connectivity were correlated with changes in pressure pain threshold. * p<0.05 pairwise t-test. Abbreviations: RA, real acupuncture; SA, sham acupuncture; VGAIT, video-guided acupuncture imagery treatment; RV, VGAIT; SV, VGAIT control; FC, functional connectivity.

3.4 Functional and structural brain metrics indicate treatment responses

For real acupuncture, among the 8 derived CVs, the second CV (CV2) was found to correlate with

changes in heat pain threshold on the leg for both ReHo (r = 0.44, p = 0.03) and GMV (r = -0.43, p =

0.04). As displayed in Figure 6 upper panel, the spatial maps were transformed into Z values, visualized

at |Z|>3. The identified regions in ACU_ReHo_CV2 include the putamen, caudate, thalamus,

hippocampus, and brainstem. The regions in ACU_GM_CV2 include the medial prefrontal cortex

18

(mPFC), anterior cingulate cortex (ACC), middle cingulate cortex (MCC), posterior cingulate cortex (PCC), thalamus, hippocampus, caudate, and dorsal lateral prefrontal cortex (DLPFC). Common in ACU_ReHo_CV2 and ACU_GM_CV2, subcortical regions including the thalamus, hippocampus, and striatum, which are parts of basal ganglia circuitry, indicate a participant's responsiveness to acupuncture treatment. Participants with better treatment responses had lower GMV in the cingulate cortex (anterior, middle, and posterior), mPFC, and DLPFC.

For VGAIT (Figure 6 lower panel), the second CV (CV2) was found to correlate with changes in pressure pain threshold on the leg for both ReHo (r= -0.50, p = 0.03) and GMV (r = -0.44, p = 0.04). The identified regions in VGAIT_ReHo_CV2 include the insula, supplementary motor area (SMA), rostral anterior cingulate cortex (rACC), and brainstem. The regions in VGAIT_GM_CV2 include the insula, hippocampus, and paracentral lobule (ParaCL). Common in VGAIT_ReHo_CV2 and VGAIT_GM_CV2, the lower the ReHo value and GMV in the insula (the anterior portion in particular), the larger the changes in pain threshold after VGAIT.
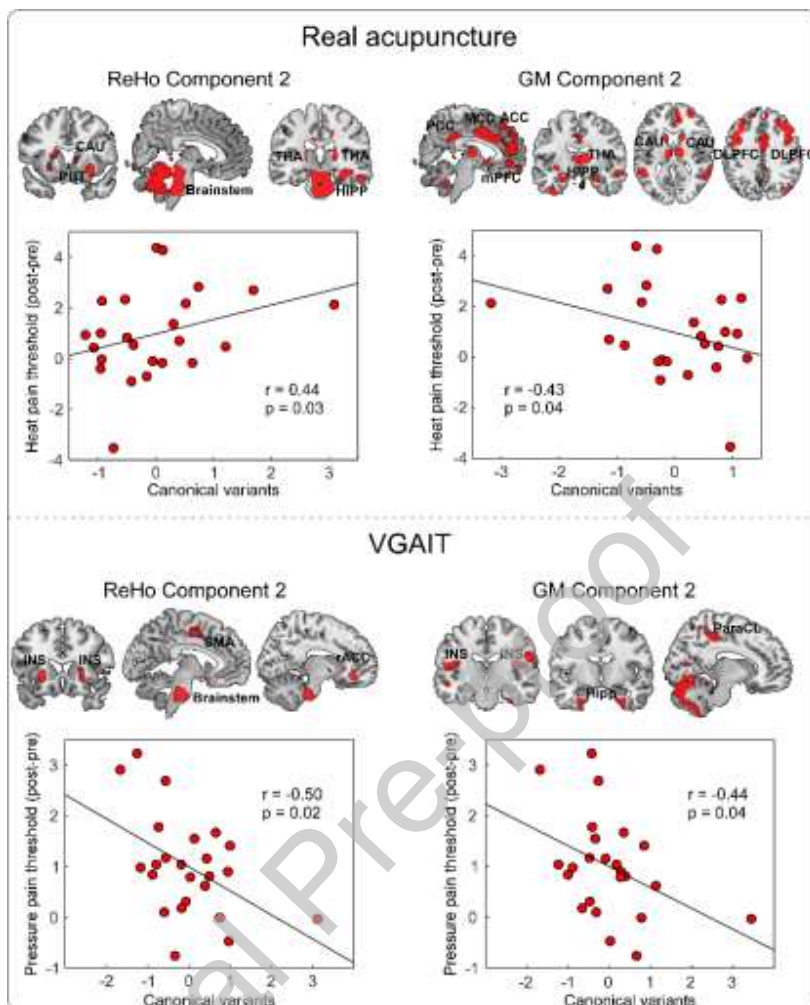
Figure 6. Joint components significantly correlated with treatment responses. Upper panel: The joint components ACU_ReHo_CV2 and ACU_GM_CV2 were significantly associated with changes in heat pain threshold on the leg after acupuncture treatment. Lower panel: The joint components VGAIT_ReHo_CV2 and VGAIT_GM_CV2 were significantly associated with changes in pressure pain threshold on the leg after VGAIT. Abbreviations: CAU, caudate; PUT, putamen; THA, thalamus; HIPP, hippocampus; ACC, anterior cingulate cortex; MCC, middle cingulate cortex; PCC, posterior cingulate cortex; mPFC, medial prefrontal cortex; DLPFC, dorsal lateral prefrontal cortex; INS, insula; SMA, supplementary motor area; rACC, rostral ACC; ParaCL, paracentral gyrus; VGAIT, video-guided acupuncture imagery treatment. p values for correlations are not corrected.

4. Discussion

In the present study, we first investigated the modulatory effects of acupuncture and VGAIT on pain threshold and intrinsic brain connectivity. Both real acupuncture and VGAIT significantly increased participants' pain thresholds, compared to their corresponding control conditions (i.e., sham acupuncture and VGAIT control). We found that real acupuncture significantly decreased both intra- and inter-regional connectivity in sensorimotor areas and that these reductions in connectivity were associated with participants' altered pain thresholds. In contrast, VGAIT significantly increased intra-regional connectivity in the striatum and inter-regional connectivity between subcortical and default mode networks. These enhanced connectivities were correlated with participants' increased pain thresholds. We then tested the hypothesis that a participant's responsiveness to acupuncture and VGAIT might be jointly encoded by state and trait brain characteristics. Using pre-intervention functional (ReHo) and structural (GMV) brain metrics as features and a multimodality fusion approach, we identified joint components that explained interindividual variabilities in pain threshold changes after real acupuncture and VGAIT, respectively. These findings demonstrated the acute modulatory effects of acupuncture and VGAIT and suggest that both could be promising complementary therapeutic approaches for relieving pain.

During the acupuncture sessions, participants were supine in the scanner and could not see the needle. At initiation of the real and sham acupuncture interventions, we specifically asked participants whether they could feel the needle sensation. Manipulation continued until participants confirmed that they felt needle sensation. There was no significant difference between expectancy scores after real and sham acupuncture, which suggests that participants were not able to distinguish real from sham acupuncture (Cao et al., 2019). In other words, the different types of acupuncture did not influence patient expectations, a key component of the placebo effect (Jian Kong et al., 2006; Streitberger and Kleinhenz, 1998; White et al., 2003).

Previous studies suggest that acupuncture analgesia may work through diffuse noxious inhibitory controls (DNIC), which is the response from a painful stimulus that inhibits pain from another stimulus (i.e., pain-inhibiting-pain effect) (Bing et al., 1990; Murase and Kawakita, 2000; Tobbackx et al., 2013). A previous study of healthy individuals investigated the analgesic effect of acupuncture, compared to nonpenetrating sham acupuncture and cold-pressor-induced DNIC. The authors found that acupuncture needling at low pain stimulus intensity was not comparable with a DNIC-like effect in healthy and pain- free individuals (Schliessbach et al., 2012). In the present study, participants' ratings for sharp pain (1.44 ± 0.37 for real acupuncture, 1.00 ± 0.30 for sham acupuncture, 0.10 ± 0.05 for VGAIT, and 0 for VGAIT control), and dull pain (1.98 ± 0.38 for real acupuncture, 0.96 ± 0.27 for sham acupuncture, 0.48 ± 0.19 for VGAIT, and 0 for VGAIT control) can be considered to indicate mild sensations produced by the interventions (see Supplementary Figure 3 for detailed comparisons of each sensation rating for the different interventions). Therefore, we believe that the analgesia effects by acupuncture and VGAIT observed in our study are unlikely produced through a DNIC mechanism.

4.1 Real acupuncture and VGAIT modulated intrinsic brain connectivity.

Pre-intervention intra- and inter-regional brain connectivity were not significantly different across the four sessions. We observed substantial between-session and within-subject stability of functional brain connectivity over the approximately one month of interventions (Finn et al., 2015; Tu et al., 2019b). It is worth mentioning that each intervention was separated by at least 7 days (i.e., wash-out period). Therefore, pre-intervention baseline measures were unlikely to be affected by the previous sessions.

In contrast, our findings indicate that real acupuncture and VGAIT influenced different brain regions and networks within the respective sessions, demonstrating the neural plasticity of the human brain. Consistent with previous findings, real acupuncture significantly modulated sensorimotor areas (e.g., primary somatosensory cortex) and network in both healthy (Dhond et al., 2008; Dong et al., 2014; Jiang et al., 2013) and patient populations (Chen et al., 2015). Decreased connectivity with sensorimotor areas

22

may support lower sensitivity to pain/anti-nociceptive processing and thereby increase pain threshold. In contrast, VGAIT activated the dorsal striatum (i.e., putamen), which is a key structure in the basal ganglia and notably contributes to the shaping of subjective pain experience (Bingel et al., 2004; Borsook et al., 2010; Starr et al., 2011). A previous study has shown that individuals with lesions involving the putamen had reduced pain sensitivity and pain-related cortical activity (Starr et al., 2009). In addition, the basal ganglia interacts with cortical activities via the cortico-basal ganglia-thalamo-cortical loops and is associated with pain and pain-related affective processing (Borsook et al., 2010; Chudler and Dong, 1995). Our results suggest that enhanced connectivity between basal ganglia subcortical structures and the DMN following VGAIT is associated with pain threshold changes. Thus, plasticity in basal ganglia-DMN circuitry may change the way nociceptive signals are appraised and evaluated (Baliki et al., 2012), and relieve pain through self-regulation (Reddan and Wager, 2019).

It is worth noting that findings from the present work, which focused on pre- and post-intervention brain connectivity differences, are relevant to our previous work investigating the modulatory effects of acupuncture/VGAIT during administration of the intervention (i.e., task-related intervention-evoked brain activity) (Cao et al., 2019). During acupuncture stimulation, the insula was activated to integrate sensory and affective information and produce analgesic effects (Cao et al., 2019). The insula communicates with other brain regions during acupuncture, especially sensorimotor areas (Flodin et al., 2014; Kim et al., 2017), which may lower local and regional synchronization in sensorimotor areas after acupuncture, as was observed in the present study. During VGAIT, the rACC/mPFC, a key region of the DMN, was deactivated by imagining while recalling the acupuncture needle stimulation experience and sensations. Note that deactivation corresponds to stronger DMN activity, since the DMN is always suppressed when performing tasks. Such deactivation of the prefrontal portion of the DMN during VGAIT may have changed the neural plasticity in basal ganglia-DMN circuitry and changed the local connectivity in the putamen and inter-regional connectivity between basal ganglia and the DMN.

Comparing modulatory effects of real acupuncture and VGAIT, we found that real acupuncture mainly *deactivated* brain connectivity (Figure 4A and Figure 5B), whereas VGAIT *activated* brain connectivity (Figure 4B and Figure 5C). This is interesting as it suggests that there are two different analgesic mechanisms underlying the efficacy of acupuncture and VGAIT. Acupuncture may achieve this goal by directly reducing excitability in pain-related brain regions (i.e., sensorimotor), while VGAIT may strengthen communication between basal ganglia subcortical regions and prefrontal higher-order areas, which adjusts participants' affective experience and control of pain perception.

4.2 Individual differences in analgesic effects

Participants who had strong analgesic responses following acupuncture did not necessarily respond similarly to VGAIT and there was no significant association of behavioral responses (i.e., changes of pain threshold) between acupuncture and VGAIT. This would suggest that different brain mechanisms underlie responses to these two interventions. The joint analysis of fMRI and sMRI, and their associations with pain threshold changes, enable us to determine how multimodal integration relates to state and trait brain characteristics that cannot be easily captured by a separate analysis of each modality (Qi et al., 2018; Sui et al., 2015).

In a recent study that examined resting-state fMRI brain connectivity, the connectivity between mPFC and basal ganglia structures was shown to predict acupuncture treatment response in chronic pain patients (Tu et al., 2019a), which is consistent with the current study's findings. The present study extends previous work by showing that intra-regional functional connectivity and GMV in the basal ganglia were jointly correlated with individual differences in pain threshold change. For sMRI only, we showed that the GMV in DMN and the attention network (i.e., DLPFC) were negatively correlated with change in pain threshold. Findings from a previous study suggest that grey matter density in areas associated with the DMN and attentional direction and shifting are inversely related to pain sensitivity (Emerson et al., 2014). Given that we tested the acute analgesic effect of acupuncture in the present study, the GMV in the

24

DMN and DLPFC may also represent participants' unique pain threshold, which influenced the pain threshold changes resulting from acupuncture.

Anterior insula, which was evident in both functional and structural components, was found to be related to VGAIT responsiveness. VGAIT is an intervention that relies heavily on imagery. Anterior insula is one of the most important brain areas underlying imagery processing (Jabbi et al., 2008; Lucas et al., 2015) and may, therefore, reflect individual's ability to actively engage with VGAIT, as compared to passively receiving acupuncture. One's ability to engage with VGAIT would undoubtedly influence treatment response. For ReHo only, we observed that the rACC ReHo values can predict VGAIT response, which may be linked to deactivation of rACC during application of VGAIT (Cao et al., 2019).

The contributions of the hippocampus in shaping participants' responses were observed in both acupuncture and VGAIT intervention conditions. This finding suggests that the acute analgesic effects produced by these two interventions may depend on participants' learning and memory abilities (Dhond et al., 2008). In addition, reduced hippocampus volume has been reported in chronic pain patients, suggesting possible deficits in emotion and cognitive brain systems (Mutso et al., 2012). The efficiency of emotion and cognitive brain systems, partially reflected by hippocampal activity and structure, may also underlie participants' response to pain treatments.

4.3 Limitations and future directions

The present work was only able to assess acute analgesic effects of acupuncture and VGAIT. The long-term effects of the intervention, especially on chronic pain patients, remain unknown. Future studies with chronic pain patients and more intervention sessions are necessary to establish the long-term efficacy of VGAIT and acupuncture. Although we used a cross-over, within-subject design, the sample size is modest in the present study. A future study with a larger sample size is needed to establish reliability of the findings.

4.4 Conclusion

We found that acupuncture and VGAIT produce analgesic effects and that these effects appear to be modulated by different intra- and inter-regional brain connectivities. The effectiveness of acupuncture and VGAIT were encoded by different functional and structural brain metrics. Elucidating the underlying mechanisms associated with the efficacy of different pain interventions may facilitate the development of new and more effective pain therapies.

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Author contributions

J.K designed the study. J.C and J.K performed the study. Y.T and J.C analysed the data. Y.T and J.C wrote the paper. J.K, S.O and G.W revised and approved the final manuscript.

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