Acupuncture treatment of chronic low back pain reverses an abnormal brain default mode network in correlation with clinical pain relief

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ABSTRACT

Background  Acupuncture is gaining in popularity as a treatment for chronic low back pain (cLBP); however, its therapeutic mechanisms remain controversial, partly because of the absence of an objective way of measuring subjective pain. Resting-state functional MRI (rsfMRI) has demonstrated aberrant default mode network (DMN) connectivity in patients with chronic pain, and also shown that acupuncture increases DMN connectivity in pain-modulator and affective-emotional brain regions of healthy subjects.

Objective  This study sought to explore how cLBP influences the DMN and whether, and how, the altered DMN connectivity is reversed after acupuncture for clinical pain.

Methods  RsfMRI data from 20 patients with cLBP, before and after 4 weeks of treatment, and 10 age- and gender-matched healthy controls (without treatment) were analysed using independent components analyses to determine connectivity within the DMN, and combined with correlation analyses to compute covariance between changes in DMN connectivity and changes in clinical pain. Visual analogue scale data were assessed to rate clinical pain levels.

Results  Less connectivity within the DMN was found in patients with cLBP than in healthy controls, mainly in the dorsolateral prefrontal cortex, medial prefrontal cortex, anterior cingulate gyrus and precuneus. After acupuncture, patients’ connectivities were restored almost to the levels seen in healthy controls. Furthermore, reductions in clinical pain were correlated with increases in DMN connectivity.

Conclusions  This result suggests that modulation of the DMN by acupuncture is related to its therapeutic effects on cLBP. Imaging of the DMN provides an objective method for assessment of the effects of acupuncture-induced analgesia.

INTRODUCTION

Chronic pain disorders involve pain that persists beyond the healing phase after an injury.1 Chronic low back pain (cLBP) is a common chronic pain disorder and defined as pain in the lumbosacral area of the spine. In over 85% cases of cLBP, the cause is ‘non-specific’, and in many cases is associated with other chronic symptoms.2 Only 10–15% of cases are caused by structural spine disorders.3

Acupuncture has become a popular treatment for patients with cLBP because it has been shown to relieve pain effectively.4 5 In most studies in this field, the efficacy of acupuncture treatment for cLBP is measured by the patient’s self-reported pain. Since chronic pain is a subjective sensation, objective observation of chronic pain is particularly difficult. Elucidation of the mechanism of acupuncture treatment is imperative to establish its theoretical basis.

Recent research using brain-imaging studies of pain has focused on alterations in brain activation, rather than the peripheral dysfunctions, associated with cLBP,16 and indicated that effective treatment should reverse abnormal brain activity.7

Most previous functional MRI studies of the brain-based mechanisms of chronic pain or acupuncture analgesia have concentrated on changes evoked by stimuli, such as the decreased deactivation that occurs during the execution of a task and the increased connectivity during pain stimuli.8 9 These studies have not been performed during the resting state, but during needle stimulation with an acupuncture needle, often in healthy people.10 11 Few have focused on post-
therapeutic effects on chronic pain. Indeed, assessments of changes elicited by external stimuli (pain or acupuncture) do not equate to assessments of chronic pain or post-treatment relief of chronic pain because chronic pain is characterised by ongoing, spontaneous and intrinsic pain and is thus difficult to reliably elicit. The effects of acupuncture stimuli may not be separating the concurrent brain activity related to the sensory stimulation (ie, the needling of acupuncture points) from the brain activity associated with the therapeutic effects that result from the same stimulation.

Imaging studies of resting-state brain regions in healthy people have shown correlated activity that is known as the intrinsic ‘functional connectivity’ network. One important network related to pain and cognition is the ‘default mode network’ (DMN), which is more active during rest than during exposure to external stimuli. The connectivity maintains functional coupling of brain regions within the DMN, which is measured by the spatial correlation in activity between anatomically disparate brain regions (eg, the medial frontal gyri, posterior cingulate cortex and precuneus, inferior parietal lobule and lateral temporal cortex, etc) at rest. The time scales for intrinsic connectivities in the low-frequency range are of the same order as the connectivities seen during spontaneous pain fluctuations, which provides additional support for the possibility of a connection between DMN connectivity and chronic pain or its modulation. More recent resting-state functional MRI (rsfMRI) data have also shown that the connectivity within the DMN is altered in some forms of chronic pain, including fibromyalgia, migraine, diabetic neuropathic pain and chronic back pain. Therefore, we propose that altered connectivity within the DMN is also associated with spontaneous chronic pain experienced by patients with cLBP. Furthermore, we propose that these alternations should be reversed by acupuncture treatment for cLBP that is associated with clinical pain relief.

RsfMRI is a relatively recently developed method that can be used to visualise the correlation between chronic pain and intrinsic connectivity of the DMN and how this connectivity is related to the ongoing pain that occurs in the resting basal state and the relief of that pain after intervention. Therefore, this method can be adopted to investigate how DMN connectivity correlates with the sustained effect of acupuncture beyond the time at which needles are taken out—that is, it can be used specifically to investigate the therapeutic effects of acupuncture.

This study focused on the spatial properties of resting-state functional connectivity in the DMN as reflected by DMN spatial component maps. First, we examined whether there were differences in DMN connectivity between healthy individuals and patients with cLBP. Second, we explored how DMN responses during rest were altered by long-term acupuncture treatment and whether the potential changes in DMN were correlated with changes in pain intensity in patients with cLBP.

MATERIALS AND METHODS

Recruitment
Ten healthy individuals (five female and five male, aged 37.7±5.1 years (mean±SD)) and 20 patients (10 female and 10 male, aged 38.1±6.4 years) with lower back pain recruited via invitation letters and telephone calls were enrolled in this study (table 1). All participants were staff of the traditional Chinese medicine (TCM) department and rehabilitation division of Huashan Hospital of Fudan University. Each participant provided written informed consent, and the ethics review board of Huashan Hospital of Fudan University approved all study protocols (ethical review No 2009-180).

Inclusion criteria
All participants were right-handed, with no history of significant medical or psychiatric disorders, and provided written informed consent. Patients had to have had continuous lower back pain and/or pain in a lower extremity for at least 3 months and to rate the intensity of their pain as ≥5 on a 0–10 VAS.

Exclusion criteria
Exclusion criteria were (1) previous acupuncture treatment for any condition, (2) previous serious spinal disorders such as tumours, infections, fractures or spinal stenosis, (3) complicated low back problem such as sciatica or prior back surgery, (4) administration of sedative or analgesic drugs within 24 h before the fMRI scan or the use of any additional pain treatments during the entire study period, including histories of taking opioid analgesics or narcotics, (5) conditions that made treatment difficult such as paralysis or seizure disorders, and (6) conditions that might confound treatment effects or the interpretation of results, including severe fibromyalgia, rheumatoid arthritis and (7) contraindications for acupuncture or MRI, including clotting and bleeding disorders, or severe psychiatric conditions and claustrophobia.

Withdrawal criteria
Subjects were allowed to leave the study unconditionally without reason and instructed to withdraw if they
were chosen: BL23 (bilateral), lower back acupuncture points in the lumbar region and lower leg week for 4 weeks (12 treatments in total).

Subjects were asked to lie in the MRI scanner, to keep their minds blank and eyes closed and to avoid falling asleep.14 The patients with cLBP were scanned twice to acquire 6.87 min of rsfMRI data for each scan, before and after the 12 acupuncture treatment treatments. The healthy group was also scanned twice, with the same interval between scans as for the cLBP group, but no acupuncture treatment was performed on this group.

Intervention
Practitioner backgrounds
Acupuncture treatment was administered by a clinical acupuncturist who has been in the TCM department of Huashan Hospital for 18 years. Assessment of pain was conducted by a doctor with 10 years of experience in the department of rehabilitation.

The needles
Sterile, disposable, 0.25 × 40 mm or 0.35 × 50 mm (diameter × length) stainless steel needles (Suzhou Medical Appliance Factory, Suzhou, People’s Republic of China) were used once. Needles were generally inserted to a depth of 5–30 mm depending on the acupuncture point, and insertion was followed by manual stimulation to elicit the de qi sensation; this stimulation consisted of twirling the needle every 15 min and just before removal of the needle at the end of the 30 min acupuncture treatment.

Clinical pain assessment
Before each scan, patients recorded pain intensity on a VAS.

fMRI
MRI data were acquired using a 3 T GE Signa VH/i MRI scanner equipped with an eight-channel head coil. T1-weighted anatomical imaging was performed using a fast spoil gradient recall sequence (TR/TE=9.27/3.78 ms, flip angle=20°, FOV=240 × 240 mm; slice thickness=1.5 mm). Blood oxygenation level-dependent functional imaging was performed using a gradient echo T2*-weighted pulse sequence (TR/TE=2000/30 ms, flip angle=90°, FOV=240 × 240 mm, 26 axial slices, slice thickness=5.0 mm with no interslice gap, matrix=64 × 64, 200 time points for a total of 6.87 min). Digital Imaging and Communications in Medicine (DICOM) image data were collected after scanning.

Image preproccessing
Data preproccessing was performed using SPM8 (statistical parametric mapping, http://www.fil.ion.ucl.ac.uk/spm/). Functional data were corrected for motion to compensate for any head movements using a linear (affine) transformation procedure (SPM-realign). Structural data were coregistered with the mean functional data (SPM-coregister) and normalised to the Montreal Neurological Institute (MNI) space using a standard MNI template (SPM-normalise). Functional data were also normalised and smoothed using a Gaussian kernel of 6 mm full width at half maximum (FWHM; SPM-smooth).

Imaging postprocessing
Independent component analysis (ICA), which can isolate the connectivities within the DMN properties from the rsfMRI data on the time-series scan, was performed on all preprocessed resting fMRI data using GIFT (Group ICA Toolbox, http://mialab.mrn.org/software/gift/) software. Independent component (IC) maps in the form of a z statistic were created, and the temporal coherence of activated/deactivated areas was examined with these maps. For each participant, an IC map of the DMN was extracted from the fMRI using the spatial correlation between the DMN template made by our group and the IC map.

Statistical analysis
One-sample t tests were performed to derive group maps of DMN connectivity, paired-sample t tests were performed to compare the changes in DMN connectivity before and after acupuncture in the patients with cLBP, and independent-sample t tests were performed to compare changes in DMN connectivity in the patients with cLBP before acupuncture with those of the normal controls. A cluster-corrected p<0.05 level was used as the threshold for statistical significance. Spearman rank order correlations between the clinical pain intensities (as measured on the VAS) of the patients with cLBP and the voxel numbers of the DMN property IC maps were obtained from the rsfMRI data (both before and after acupuncture) to investigate the relationship between changes in pain intensity and changes in DMN connectivity.

RESULTS
The data from two sessions of rsfMRI were collected from all 10 healthy controls and 18 patients who completed 12 acupuncture treatment sessions; two patients withdrew because they had taken analgesic medication. The acquired data met the requirements for data processing, and the relevant DMN images were generated.
The main cLBP pain ratings were 5.95 (median 6; range 4–8) before treatment and 1.20 (median 1; range 0–2) after treatment, a significant difference (T=610, p<0.001, rank sum test, figure 1).

The best-fitting IC maps for the healthy controls exhibited the expected anatomical scopes of the DMN connectivity at rest within the inferior parietal lobule, posterior cingulate cortex and medial areas of the inferior, middle and superior frontal gyri and the precuneus (figure 2A).

DMN connectivities in the patients with cLBP versus the healthy groups showed reductions of this network in the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPFC), anterior cingulate gyrus (ACC) and precuneus before treatment (figure 2B). After acupuncture treatment, the DMN connectivities in the patient group were almost identical to those of the control group. (figure 2C)

Specifically, the connectivities of the DLPFC, MPFC, ACC and precuneus were increased in the post-acupuncture scan relative to the pre-acupuncture scan in the cLBP group.

The mean number of voxels with DMN properties in the control group was 2047 and in the cLBP group was 1739 and 1998 before and after treatment, respectively; this difference was significant (p<0.01, figure 3).

The correlation between the pre- and post-treatment differences in the mean numbers of voxels with DMN properties and the pre- and post-treatment differences in the spontaneous pain ratings of the patients with cLBP was statistically significant (r=−0.805, p<0.01, figure 4).

DISCUSSION

Our main findings showed that patients with cLBP exhibited abnormalities in DMN connectivities during rest in comparison with the healthy controls; these abnormalities encompassed the DLPFC, MPFC, ACC and precuneus and were restored to normal after acupuncture treatment. Furthermore, reductions in clinical pain were positively correlated with increase in DMN connectivity.

Connectivity within the DMN is influenced and disrupted during rest in patients with frequent ongoing pain attacks.17 23 The ICA method we used extracted DMN properties (mean voxel numbers) from fMRI data that reflected connectivity within the DMN during rest, and this method showed that disruption of the connectivities of the DMN within the DLPFC, MPFC, ACC and precuneus can result from constant pain. This latter finding contradicts recent findings in patients with diabetic neuropathic pain or fibromyalgia, where the functional connectivities were increased across of variety of networks, including, for instance, the insula.16 19 Other studies, like ours, have shown that the ACC and insula are not functionally connected in chronic pain.23
Possibly, the insula was not seen in our study as it is not involved in DMN connectivity, although the insular cortex is commonly activated in brain-imaging studies of acute experimental pain. One study of chronic pain showed greater connectivity that extended outside of the classic boundaries of the DMN to the insula, and another study showed that the connectivity between insula and the ACC (which is a component of the DMN) was restricted in patients relative to healthy subjects. One hypothesis to explain these results is that, as the activities of the participating areas of the brain network component decreased, the shifts in the DMN extended out of the DMN to the insula and distorted the properties of the DMN. Additionally, the methods and parameters were different between these two analyses (ie, seed-based connectivity analysis was used in one of the studies), and the analgesic drugs might have influenced the results. Nevertheless, all these results indicate the value of using neuroimaging markers in the DMN to study the effects of acupuncture analgesia on chronic pain.

Studies from the same research team have shown that immediately after one acupuncture stimulation (ie, a few minutes to 30 min), connectivity in the DMN increases in pain-modulating, affective and memory-related regions such as the ACC, peri- and limbic regions in healthy people, while after long-term acupuncture plus drug treatment, connectivity between the DMN and insula is reduced in female patients with fibromyalgia. It is not known whether the long-term sustained changes found after multiple treatments in these studies are related to the immediate stimulus-related changes we have seen. To clarify this issue, 30 min acupuncture stimuli in every treatment session (in accordance with conventional acupuncture clinical practice) should be used over several weeks, and the DMN should be visualised with rsfMRI imaging technology and ICA method to examine the analgesic effects after acupuncture treatment for cLBP.

Our results show that the sustained effects of multiple treatments increased the resting DMN connectivity in patients with cLBP to levels similar to those elicited (transient sustained effects) by one stimulation in healthy controls. Interestingly, chronic pain involves the memory of pain, which can persist long after the initial pain source has been removed, and the inability to extinguish the memory of the original pain evoked can lead to centrally driven pain. We speculate that acupuncture for chronic pain that involves the transient sustained connectivity of every stimulation will transfer the pain from the DMN to affective and memory-related regions over multiple treatment sessions, which may help to erode centrally driven chronic pain memories. Therefore, we are planning to perform a study involving a long-term (4 weeks) course of acupuncture treatment and examine its therapeutic effects in rsfMRI conducted the day after the last acupuncture treatment. The study design, supported by clinical acupuncture practice, typically demands 12 sessions, regularly spaced three times a week.

In our patients with cLBP, the DMN maintained its spatial properties in the connectivity pattern of functional architecture, but was disrupted during ongoing pain attacks that affected various brain regions (the DLPFC, MPFC, ACC and precuneus) putatively involved in pain-modulatory and affective-emotional processing. It seems that chronic pain is associated with impaired cognitive abilities. We speculate that abnormal connectivity in the DMN, which is linked to self-referential cognition, is involved in processing of ongoing pain and also in modulating affective-emotional aspect of pain.

![Figure 3](http://aim.bmj.com/) The mean number of voxels with default mode network (DMN) properties in the patient group before treatment (1739) and after treatment (1998) and in the control group (2047).

![Figure 4](http://aim.bmj.com/) Scatter plot showing the relationship between the numbers of voxels with default mode network properties and VAS scores of patients. Spearman correlation = −0.805, p<0.01.
The patients with cLBP in our study had secondary symptoms of panic and anxiety, as emotional reactions. Neuroimaging has shown the influence of emotional state on pain processing, particularly in the MPFC and ACC. The ACC belongs to the affective pain matrix, and its activity is also increased during placebo analgesia. This finding suggests that the emotional effects on pain processing during treatment also contribute to analgesia. In our study, the disrupted connectivity within the DMN was involved in pain-affective processing and was reversed after acupuncture treatment.

Our results correlating decreased self-reported pain relief scores with enhanced DMN connectivity provide a neuroimaging pain-network study of the effects of acupuncture on cLBP. Thus, the clinical efficacy of acupuncture was seen and evaluated through DMN connectivity. To determine whether the observed changes in the DMN are a common signature of acupuncture treatment for chronic pain, we will study other forms of chronic pain in the future.

This study raises several points for discussion. Our results showed reduced connectivity within the DMNs of patients with cLBP and might not be generalisable to other chronic pain conditions, such as fibromyalgia and migraine. However, qualitatively similar findings have been reported. Although a VAS is a simpler method of testing for clinical pain, especially low back pain, the effects of spontaneous pain on the accuracy of VAS measures during the same time of the scan are unknown.

**CONCLUSION**

Connectivity within the DMN was used as an objective neuroimaging marker that allowed us to track pain and its relief due to the therapeutic effects of acupuncture for cLBP. This advanced approach is an example of how an understanding of the mechanisms of cLBP can be facilitated by understanding the brain correlates of the therapeutic effects of acupuncture for chronic pain.

**Summary points**

- Chronic pain is associated with an altered default mode network (DMN) connectivity.
- DMN connectivity was measured in patients with chronic back pain before and after a course of acupuncture.
- DMN was restored towards normal, in correlation with the degree of pain relief.

**Correction notice** This article has been corrected since it was published Online First. The order of the author list has been amended.

**Contributors** W-JT and JL were responsible for the study concept, design, statistical analysis and data interpretation, and wrote the draft of the manuscript. J-HZ and TY contributed to the data collection. S-WW contributed to the evaluation of patients’ pain level. J-CQ supervised the study. All authors assisted in revision of the paper.

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