NeuroImage: Clinical 23 (2019) 101885

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Multivariate resting-state functional connectivity predicts responses to real and sham acupuncture treatment in chronic low back pain

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ARTICLE INFO

Keywords:
Chronic low back pain
Acupuncture
Resting-state functional connectivity
Machine learning analysis
Treatment responses

ABSTRACT

Despite the high prevalence and socioeconomic impact of chronic low back pain (cLBP), treatments for cLBP are often unsatisfactory, and effectiveness varies widely across patients. Recent neuroimaging studies have demonstrated abnormal resting-state functional connectivity (rsFC) of the default mode, salience, central executive, and sensorimotor networks in chronic pain patients, but their role as predictors of treatment responsiveness has not yet been explored. In this study, we used machine learning approaches to test if pre-treatment rsFC can predict responses to both real and sham acupuncture treatments in cLBP patients. Fifty cLBP patients participated in 4 weeks of either real ($N = 24$, age = 39.0 ± 12.6, 16 females) or sham acupuncture ($N = 26$, age = 40.0 ± 13.7, 15 females) treatment in a single-blinded trial, and a resting-state fMRI scan prior to treatment was used in data analysis. Both real and sham acupuncture can produce significant pain reduction, with those receiving real treatment experiencing greater pain relief than those receiving sham treatment. We found that pre-treatment rsFC could predict symptom changes with up to 34% and 29% variances for real and sham treatment, respectively, and the rsFC characteristics that were significantly predictive for real and sham treatment differed. These results suggest a potential way to predict treatment responses and may facilitate the development of treatment plans that optimize time, cost, and available resources.

1. Introduction

Chronic low back pain (cLBP) is a highly prevalent and disabling disorder with unsatisfactory treatment options (Buchbinder et al., 2013; Chou and Shekelle, 2010; Deyo et al., 2006; Vos et al., 2013). Neuroimaging studies have shown functional and structural alterations in the brains of cLBP patients (Baliki et al., 2011; Kong et al., 2013b; Tagliazucchi et al., 2010a; Tu et al., 2019; Yu et al., 2014; Zhang et al., 2019), indicating the involvement of the central nervous system (CNS) in the development, maintenance, and experience of cLBP (Martucci and Mackey, 2018).

As a traditional therapeutic approach that stimulates certain points of the body with needles, acupuncture has been recommended for treating cLBP in the recent guideline of the American College of Physicians (Qaseem et al., 2017). Although the underlying mechanism of acupuncture remains elusive, accumulating evidence shows that it can relieve pain by modulating brain regions and networks associated with pain perception and modulation (Cao et al., 2018; Dhond et al., 2008; Egorova et al., 2015; Fang et al., 2009; Kong et al., 2007).

A recent meta-analysis on acupuncture treatment of chronic pain demonstrated that acupuncture is effective for cLBP, and real acupuncture is superior to placebo on average (Vickers et al., 2012, 2017). In addition, studies have also suggested that non-specific factors such as context (expectancy) may contribute to acupuncture treatment and can significantly modulate acupuncture's treatment effect (Hashmi et al., 2014; Kong et al., 2009a). Therefore, we also employed a context manipulation model by assigning patients into real or sham treatment groups with augmented or limited context (Kaptchuk et al., 2008; Lembo et al., 2009). This model enabled us to simultaneously investigate the mechanisms of acupuncture and context, as well as their

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https://doi.org/10.1016/j.nicl.2019.101885
Received 9 April 2019; Received in revised form 16 May 2019; Accepted 25 May 2019
Available online 28 May 2019

relationship, in relieving chronic low back pain.

Although acupuncture is effective for cLBP, there are large inter-individual differences in patients' responses to both acupuncture and placebo acupuncture treatment (Kong et al., 2013a). This variability is not well understood but is likely essential for elucidating the underlying mechanisms of acupuncture and placebo treatments and developing more effective treatments. A pertinent question is whether and to what extent neuroimaging metrics of the brain can provide insight into individual variation and be a reliable predictor of treatment responsiveness in clinical settings.

In this study, 50 cLBP patients underwent resting state fMRI scans before and after 4 weeks of either real or sham acupuncture treatment with context manipulation in a single-blinded clinical trial (Kaptchuk et al., 2008). We explored whether pre-treatment FC could predict symptom changes (measured by cLBP severity scores and comorbid physical, mental, and social symptoms) following real and sham treatment using cross-validated machine learning techniques. To increase the power and efficiency, our analyses were restricted to networks where we previously found connectivity patterns that were 1) abnormal in cLBP patients (Tu et al., 2019) and 2) potentially modulated by acupuncture (Chen et al., 2015).

2. Materials and methods

2.1. Participants

Seventy-nine patients diagnosed with cLBP with a duration of at least six months were included in the study. Fourteen patients dropped out of the study before the baseline symptom assessment and MRI session, and 11 patients dropped out of the study after the baseline assessment. Fifty-four patients received 4 weeks of real or sham acupuncture treatment with augmented or limited context (clinical trial number NCT01595451), and of those, 4 patients did not finish all treatment sessions. In total, 50 patients were included in the final analysis. The details of the study design can be found in Fig. 1. Post-treatment MRI was about one to two weeks after the last treatment session. A previous large clinical trial suggested that the effects of acupuncture can last for at least half a year (Cherkin et al., 2009). We thus believe the duration between the last treatment and the MRI scan should not influence results significantly. The inclusion and exclusion criteria for all patients can be found in *Supplementary Materials*. The Institutional Review Board (IRB) of Massachusetts General Hospital approved the study, and all experiments were performed in accordance with the guidelines set forth by the IRB for ethics and protection of human subjects.

2.2. Clinical assessment and medication

The primary clinical outcome of this study is the LBP severity assessment, which measures how bothersome a patient's LBP has been during the past week on a 0–10 visual analogue scale (VAS) from "not at all bothersome" to "extremely bothersome" (Cherkin et al., 2009; Deyo et al., 1998).

Other secondary clinical symptoms including pain interference, physical health, social disability, sleep disturbance, fatigue, depression, anxiety, and pain intensity in the past week were measured using the Patient Reported Outcomes Measurement Information System (PROMIS) (Cella et al., 2007, 2010). In addition to PROMIS, patients' depression symptoms were assessed with the Beck Depression Inventory (BDI).

All participants were allowed to continue their existing medication. Medication use per self-report was limited to non-steroidal anti-inflammatory drugs (e.g., ibuprofen) and acetaminophen (e.g., Tylenol). Six out of 50 patients took opioid analgesics during the study (2 and 4 patients in real and sham treatment groups, respectively). Additional non-pharmacological methods of self-reported pain management included chiropractic massages, physical therapy, and exercise.

2.3. MRI acquisition

All MRI data were acquired using a 32-channel radio-frequency head coil in a 3 T Siemens scanner at the Massachusetts General Hospital Martinos Center for Biomedical Imaging. During the resting-state fMRI, subjects were asked to keep their eyes open and to blink normally while looking at a darkened screen for approximately 6 min. A whole-brain gradient-echo echo-planar-imaging sequence was used for functional scanning with a repetition time (TR) of 3000 ms (30 ms echo time, 44 3.0 mm-thick slices, 2.6 × 2.6 mm in-plane resolution), and a total of 125 volumes were collected. A high-resolution, T1-weighted structural image (1 mm^3 isotropic voxel MPRAGE) was acquired after functional imaging.

2.4. Acupuncture treatment

Patients were randomized into one of four groups ('augmented context' real acupuncture; 'limited context' real acupuncture; 'augmented context' sham acupuncture; 'limited context' sham acupuncture) using a permuted block randomization method with equal probability of being assigned to each group, and they received 6 treatment sessions over 4 weeks (twice a week for 2 weeks and then once a week for 2 weeks). All patients and study staff were blinded to the treatment groups. Only the acupuncturists were not blinded.

The 7 real acupoints used were Yaoyangguan (GV3), bilateral Shenshu (BL23), bilateral Weizhong (BL40), bilateral Taixi (KI3), and 1–3 ashi points bilaterally on the lower back and legs. Each treatment lasted 25 min and was performed by a licensed acupuncturist, with additional stimulation applied to elicit "deqi" by twirling the needles at 10 min and again just prior to needle removal. 12 sham acupoints were selected for the placebo acupuncture treatment using a Streitberger placebo acupuncture needle (Supplementary Materials and Fig. S1). The rationale for the selection of these acupoints has been published in a previous clinical trial protocol on acupuncture treatment of low back pain (Sherman and Cherkin, 2003).

Patients randomly assigned to the augmented context group experienced a structured interaction with the acupuncturist lasting around 30 min using a method applied in a previous study (Kaptchuk et al., 2008). The acupuncturist's interaction with the subject was structured with respect to both content (conversations between the acupuncturist and patient involved four primary topics of discussion) and style (five primary behaviors). The topics of discussion included questions concerning 1) LBP symptoms; 2) other medical symptoms; 3) psychosocial history, Chinese medicine intake and how cLBP has affected the patient's relationships and lifestyle, and 4) how the patient understands the "cause" and "meaning" of his or her condition. The acupuncturist incorporated four primary behaviors including: 1) exuding a warm, friendly manner; 2) active listening (such as repeating the patient's words, asking for clarifications); 3) empathy (such as saying "I can understand how difficult cLBP must be for you"); 4) 20 s of thoughtful silence while feeling the pulse or pondering the treatment plan; and 5) communication of confidence and positive expectation ("I have had much positive experience treating cLBP and look forward to demonstrating that acupuncture is a valuable treatment in this trial"). The subject also received physical contact from the acupuncturist during the Chinese medicine intake. For the augmented context, the acupuncturist had a checklist to ensure that all key points were covered.

In the limited context group, the acupuncturist merely read study information to the patient and aimed to "converse with patients as little as possible." We used the expectations for relief scale (ERS), a 0–10 scale with 0 indicating a very negative expectation of "does not work at all" and 10 indicating a very positive expectation of "complete pain relief" to measure the expectation of patients for acupuncture treatment at baseline and after Treatments 1, 4, and 6. The details of the context

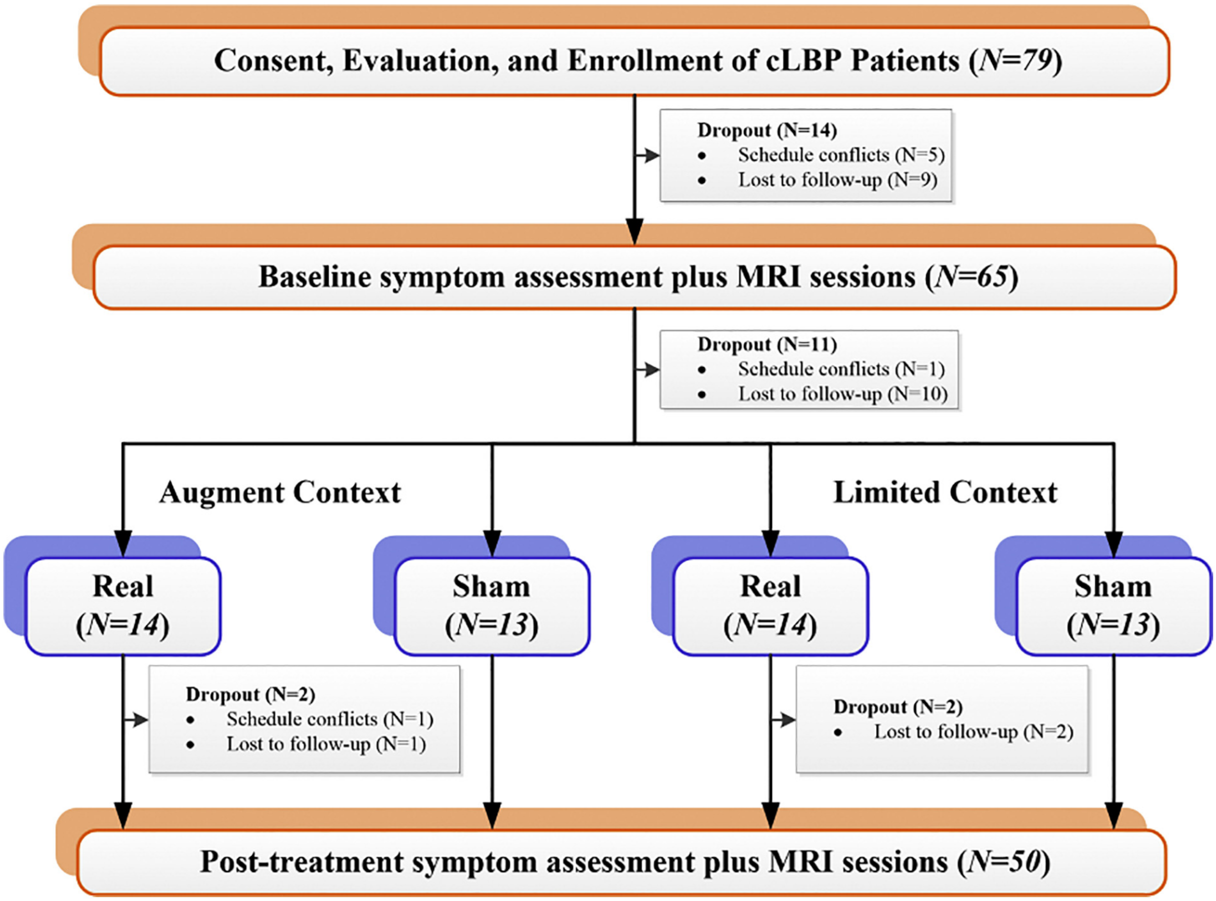

Fig. 1. Experimental procedures. 50 cLBP patients were included in the analysis. Patients received 4 weeks of longitudinal real or sham acupuncture treatment. Clinical assessments and MRI scans were collected at baseline and after all treatment sessions.

manipulation can be found in the *Supplementary Materials* and in our previous publication (Kaptchuk et al., 2008).

2.5. fMRI preprocessing

The fMRI data were preprocessed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). The first five volumes were discarded for signal equilibration. Images were slice-timing corrected and realigned. The resulting images were normalized to the Montreal Neurological Institute (MNI) space (Ashburner and Friston, 2005) and spatially smoothed using a Gaussian kernel of 5 mm full width at half maximum (FWHM). To minimize the effect of head motion on the estimation of functional connectivity, we followed a strategy suggested by a recent benchmark study (Ciric et al., 2017) by combing the 6 motion estimates and 2 physiological time series (white matter and cerebral spinal fluid [CSF]) as nuisance parameters and regressing them out from the whole-brain fMRI data for denoising. To rule out potential association of head motion and chronic pain symptoms, we calculated the correlation between maximal framewise displacement (FD) value (Power et al., 2012) and cLBP severity scores. Detailed results can be found in *Supplementary Materials*.

2.6. Definition of seeds and functional connectivity construction

To examine whether baseline FC could predict symptom changes following acupuncture treatment, we selected 30 brain regions, which were defined using group independent component analysis in our previous study (Tu et al., 2019), from four key resting-state networks. Specifically, these networks included the default mode network (DMN), sensorimotor network (SMN), salience network (SN), and central executive network (CEN). The brain of the cLBP patient is continuously processing spontaneous background pain by integrating information between these networks that are related to sensory, cognitive, and emotional functions (Baliki et al., 2008; Borsook et al., 2013; Kong et al., 2013b; Kucyi and Davis, 2015), and the FC between these regions have shown close association with cLBP clinical symptoms and may capture the characteristics of cLBP pathophysiology (Tu et al., 2019). Thus, we used these brain regions as seeds to contruct FC matrices for prediction analyses. The details of the spatial map and peak coordinates of each brain region are provided in Fig. S2-S5 and Table S1.

The FC matrix was constructed based on the time courses of seeds by calculating pairwise Pearson's correlations among time courses and z-transforming. Since the FC matrix was symmetric, in total we had 435 ($=30 \times 29/2$) connectivity patterns across four networks for further investigation.

2.7. Predict treatment response from baseline fMRI

We used the pre-treatment multivariate FCs as features to predict treatment responses (changes in pain severity after 4 weeks) for both real and sham treatment groups. One aim of this study was to investigate the role of context in acupuncture treatment. Unfortunately, we failed to modulate patients' expectations and treatment responses in the present study (see Results and Discussion for details). Thus, we pooled augmented and limited context groups and focused our prediction analyses on real ($N = 24$) and sham ($N = 26$) groups.

Previous studies have suggested that different mechanisms may underlie real and sham acupuncture (Egorova et al., 2015; Harris et al., 2009; Kong et al., 2009a). We therefore built multivariate linear regression models with changes of pain severity as dependent variables (responses) and multivariate FCs ($N = 435$) as independent variables (predictors) for real and sham treatment, respectively. Such models have been widely used in fMRI studies to identify brain patterns related to behavior and disease (Hu and Iannetti, 2016; Lindquist et al., 2017; Tu et al., 2016a, 2016b, 2018a; Wager et al., 2011). We decoded the models using support vector regression (SVR, implemented by LIBSVM) (Chang and Lin, 2011), resulting in a pattern of prediction weights across all FCs, and the significance of each FC in prediction was assessed using bootstrap testing (see *Statistical Analysis* for details).

The prediction was based on 5-fold cross-validation to ensure separation between training and testing samples. Specifically, we partitioned all subjects into five groups and used four groups for training and one group for testing. This procedure was repeated 5 times to ensure that each subject was used as the test sample once and that the model did not include information from the test samples. We used an SVR with a radial basis function (RBF) kernel. Two parameters, cost value and gamma in RBF kernel, were optimized using a grid search via inner cross-validation. The predicted treatment responses were calculated by taking the dot product of the prediction weights (obtained from training samples) and FC values from subjects in test samples.

To assess prediction performance, we calculated the squared prediction-outcome correlation (R^2) (Wager et al., 2013), which was defined as the squared correlation between the actual and predicted treatment responses, as well as the mean absolute error (MAE), which was defined as the mean discrepancy between actual and predicted treatment responses (Huang et al., 2013; Tu et al., 2018b). The significance of the prediction performance was measured by permutation testing (see *Statistical analysis* for details).

To obtain reliable performance and reduce the potential bias from cross-validation (e.g., there might have been systematic difference across the randomly partitioned folds, yielding biased results when concatenating across folds), we ran 5-fold cross-validation 100 times and reported the mean and standard deviation of the performance measure.

2.8. Predict changes of different symptoms for cLBP

To explore the prediction of different clinical domains and comorbid symptoms, the multivariate linear regression model was also used to predict changes in PROMIS sub-scores, including pain intensity, pain interference, anxiety, depression, fatigue, sleep disturbance, and social disability in the past week. To avoid collinearity between PROMIS sub-scores, we trained the multivariate prediction model separately for different symptoms and used the square of prediction-outcome correlation (R^2) as the measure for capturing behavioral variance across subjects.

2.9. Statistical analysis

2.9.1. Clinical outcome

We used a two-way analysis of covariance (ANCOVA) with treatment (real vs. sham) and context (augmented vs. limited) as factors to investigate the difference in treatment responses between groups with age, gender, and duration of pain included as covariates of no interest.

Based on recent meta-analysis results showing real acupuncture's superior performance to sham acupuncture (Vickers et al., 2012, 2017) and results from a previous study on context effect (Kaptchuk et al., 2008), we only wanted to test (1) whether real acupuncture can produce greater pain reduction than sham acupuncture (i.e., real > sham); and (2) whether the augmented context groups can produce greater pain reduction than the limited context groups (i.e., augmented > limited). Thus, a one-tailed hypothesis *t*-test was applied to assess the above hypothesis.

2.9.2. Permutation testing

In permutation testing, we randomly permuted the labels of the data (treatment response) prior to training. Cross-validation was then performed on the permuted dataset, and the procedure was repeated 1000 times. If the model trained on real data labels had a prediction-outcome correlation (z-scored) and an MAE that exceeded the 95% confidence interval generated from the results of the models trained on randomly relabeled data labels, the prediction model was considered to be performing well.

2.9.3. Bootstrap testing

To threshold and select the most predictive features, we constructed 1000 bootstrap samples (with replacement) consisting of paired FC features and treatment responses and ran SVR analysis on each. A one sample t-test was performed for each feature based on the proportion of weights below or above zero.

3. Results

3.1. Treatment effects on cLBP patients

No significant difference between the four treatment groups was found for age ($F_{3,46} = 0.77$, $p = 0.52$), gender ($\chi^2 = 0.59$, $p = 0.90$) or duration of back pain ($F_{3,46} = 0.22$, $p = 0.88$). Patients' pain severity scores after all treatments were reduced significantly in all four groups ('Augmented real': −2.4 ± 1.5; 'Augmented sham': −1.6 ± 2.4; 'Limited real': −3.2 ± 2.5; 'Limited sham': −1.8 ± 2.3; Table 1). ANCOVA results showed no significant main effect for treatment, context, and their interaction. A one-tail t-test showed real acupuncture

Table 1
Clinical outcome changes after acupuncture treatments (Post-Pre).

Treatment mode	N	Age	Duration (years)	Pain Severity Change	P
Augmented real	12 (4 males)	43.0 ± 11.1	6.0 ± 4.1	−2.4 ± 1.5	< 0.001
Augmented sham	13 (5 males)	40.0 ± 13.5	7.2 ± 3.8	−1.6 ± 2.4	0.03
Limited real	12 (4 males)	35.0 ± 13.2	5.9 ± 5.9	−3.2 ± 2.5	< 0.001
Limited sham	13 (6 males)	40.0 ± 14.4	6.5 ± 5.4	−1.8 ± 2.3	0.01

ANCOVA	Sum of squares	df	F	P
Main effect				
Treatment	15.4	1	3.06	0.09
Context	3.8	1	0.75	0.39
Treatment × Context	1.2	1	0.24	0.63
Covariates				
Age	0.1	1	0.02	0.88
Gender	0.01	1	0.003	0.96
Duration	2.7	1	0.54	0.47

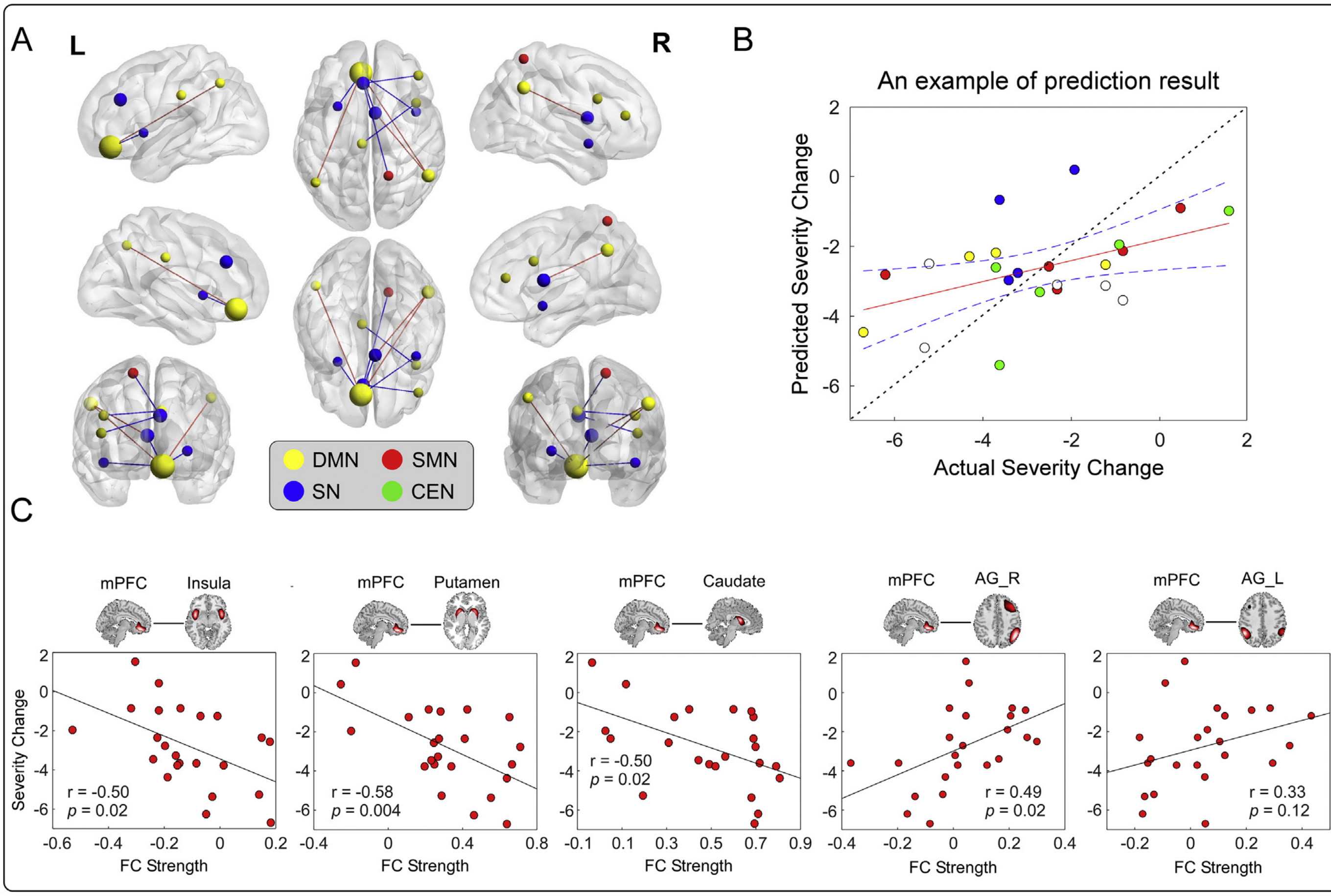

Fig. 2. Predicting the treatment effect of real acupuncture using baseline functional connectivity. Panel A shows the FCs with significantly predictive information (obtained from bootstrap testing), and the size of a node denotes its importance (number of connections) for prediction. Panel B shows an example of the performance of predicting symptom changes following real acupuncture. Different colors of dots come from different folds. The red solid line represents the relationship between the predicted and actual pain severity change, and the blue dashed lines indicate the 95% confidence interval. The prediction errors are indicated by the distance between dots and the diagonal line. Panel C shows the correlation between the strength of five identified mPFC FCs and changes in pain severity. mPFC: medial prefrontal cortex; AG_R: right angular gyrus; AG_L: left angular gyrus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

had a significantly stronger effect than sham acupuncture ($p = 0.043$), but no significant difference was observed between the augmented and limited context groups ($p = 0.21$).

A two-sample t-test showed no significant differences in expectation (measured by ERS between the augmented context and limited context groups after treatment sessions 1, 4, and 6 (Fig. S6 and Table S2).

Regression analysis showed that baseline pain severity was not significantly correlated with treatment responses (real: $r = -0.19$, $p = 0.38$; sham: $r = -0.28$, $p = 0.16$). In addition, treatment responses were not correlated with patients' pain intensity, disease duration, or BDI ($p > 0.05$ for all correlations).

3.2. Predict treatment responses

Fig. 2 shows the results of predicting the treatment responses of real acupuncture. We found that mPFC FC (mPFC-insula, mPFC-putamen, mPFC-caudate, mPFC-angular gyrus) significantly contributed to prediction, and other connectivities (posterior cingulate cortex [PCC]-middle inferior frontal gyrus [MiFG], insula-inferior frontal gyrus [IFG], insula-superior parietal lobe [SPL], and caudate-angular gyrus) between the four networks also provided significant predictive information (Fig. 2A). Fig. 2B shows an example of 5-fold cross-validation. Different colors of dots represent samples from different folds. The red solid line shows the relationship between actual and predicted pain severity change, and prediction error is represented by the distance between the dots and the diagonal line (the diagonal line indicates perfect prediction: predicted values equal to actual values).

Across 100 times of 5-fold cross-validation, the prediction model obtained a squared correlation of $R^2 = 34.3 \pm 5.5\%$ ($p = 0.033$) between actual and predicted treatment responses and an MAE of 1.67 ± 0.02 ($p = 0.023$) for real acupuncture. Greater decreases in pain severity correlated significantly with stronger pre-treatment mPFC-SN FC (mPFC-insula: $r = -0.50$, $p = 0.02$; mPFC-putamen: $r = -0.58$, $p = 0.004$; mPFC-caudate: $r = -0.50$, $p = 0.02$; Fig. 2C) and weaker pre-treatment mPFC-angular gyrus FC ($r = 0.49$, $p = 0.02$ and $r = 0.33$, $p = 0.12$ for right and left angular gyrus, respectively).

For sham acupuncture (Fig. 3A), we also found that mPFC FC (mPFC-dACC, mPFC-SPL, mPFC-paracentral lobe [ParaCL]) and other connections across four networks (superior frontal gyrus [SFG]-precentral gyrus [PreCG], SFG-MiFG, and anterior cingulate cortex [ACC]-ParaCL) provided significant information for prediction. Fig. 3B shows an example of 5-fold cross-validation. Across 100 times of cross-validation, we obtained a squared correlation of $R^2 = 29.3 \pm 5.3\%$ ($p = 0.037$) between actual and predicted treatment responses and an MAE of 1.52 ± 0.04 ($p = 0.020$) for sham acupuncture. The variances explained by the machine learning models for real and sham treatment did not differ significantly ($p = 0.52$, two sample *t*-test). Among the three aforementioned mPFC FC showing significantly predictive information, we only found that the strength of mPFC-dACC FC was significantly correlated with changes in pain severity.

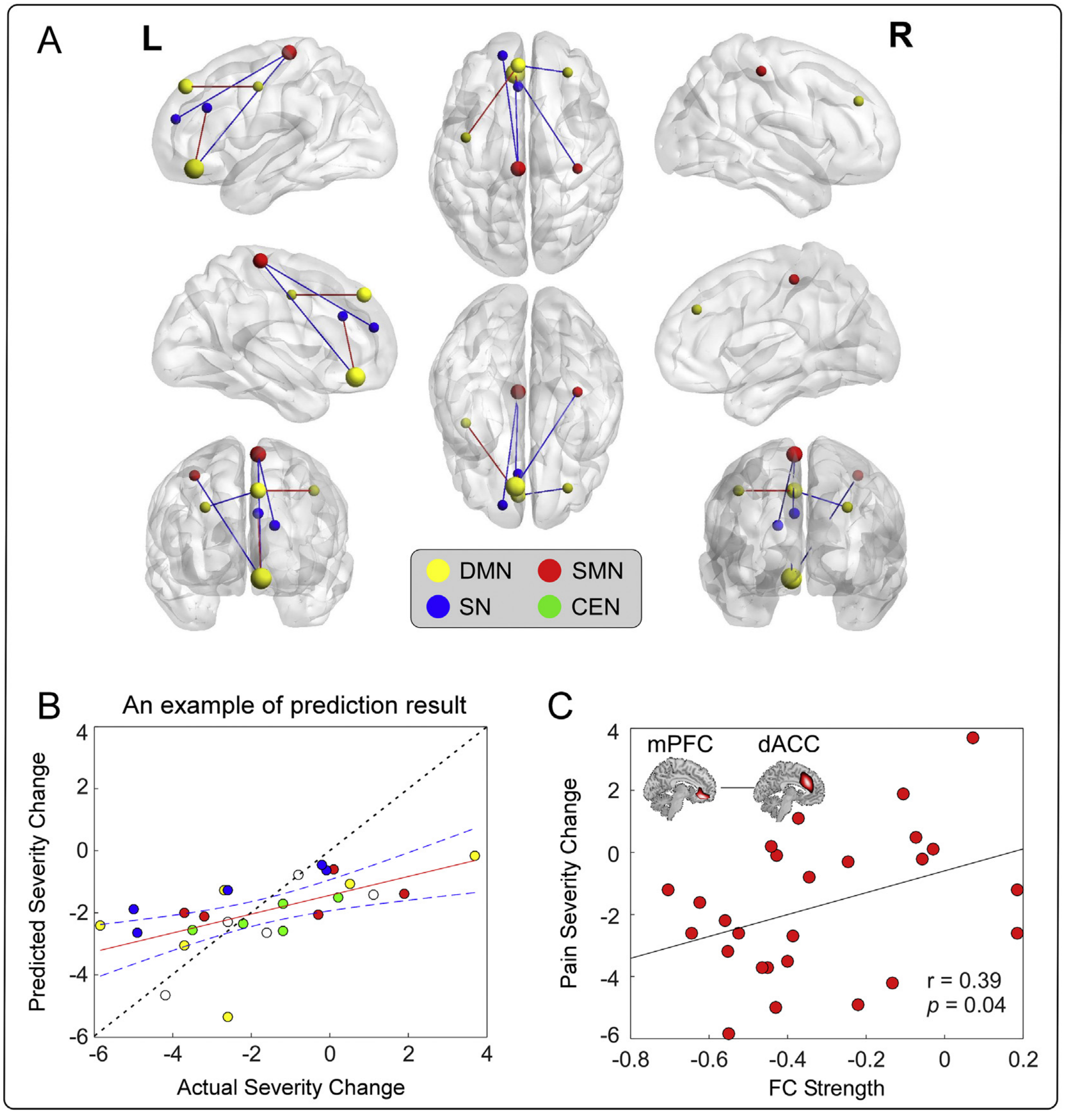

Fig. 3. Predicting the treatment effect of sham acupuncture using baseline functional connectivity. Panel A shows the FCs with significantly predictive information (obtained from bootstrap testing), and the size of a node denotes its importance (number of connections) for prediction. Panel B shows an example of the performance of predicting symptom changes following sham acupuncture. Panel C shows the correlation between the strength of mPFC-dACC FC and changes in pain severity. mPFC: medial prefrontal cortex; dACC: dorsal anterior cingulate cortex.

In addition, we included the pre-treatment cLBP pain severity scores into the prediction model and found similar prediction results (real: R^2 = 32% without vs. R^2 = 34% with; sham: R^2 = 29% without vs. R^2 = 29% with), indicating that prediction of acupuncture treatment response may be achieved by neuroimaging measures but not by initial severity.

As an exploratory analysis, we investigated the relationship between changes of pain severity and changes (post-treatment vs. pre-treatment) of FC showing predictive information at baseline, and we found that changes of FC between the mPFC and insula/left angular gyrus were significantly correlated with changes in pain severity after real treatment, while changes of FC between the mPFC and ParaCL/SPL were significantly correlated with changes in pain severity after sham treatment (Fig. S7).

Finally, we tested whether the treatment responses of real and sham intervention could be predicted through the same model. By combining neuroimaging features and symptom changes from all patients, we obtained a correlation of R^2 = 4% (p = 0.21) between actual and predicted treatment responses and an MAE of 2.11 (p = 0.34). This result suggests that different mechanisms may underlie real and sham acupuncture.

3.3. Predict changes of other symptoms

Real and sham acupuncture significantly reduced PROMIS subscores in pain intensity, physical disability and pain interference, and increased social scores (Fig. 4). We did not observe significant changes in fatigue, sleep, depression, or anxiety.

The prediction models for real treatment could significantly explain the variance of change for pain intensity (R^2 = 31.4 ± 6.0%), pain interference (R^2 = 26.5 ± 6.5%), and social scores (R^2 = 24.2 ± 6.8%), but not for physical function (R^2 = 19.7 ± 8.1%), and the models for sham treatment could account for the variance of improvements in pain intensity (R^2 = 28.3 ± 6.0%), pain interference (R^2 = 26.1 ± 6.3%), and social scores (R^2 = 23.6 ± 7.0%), but not for physical function (R^2 = 18.2 ± 8.0%).

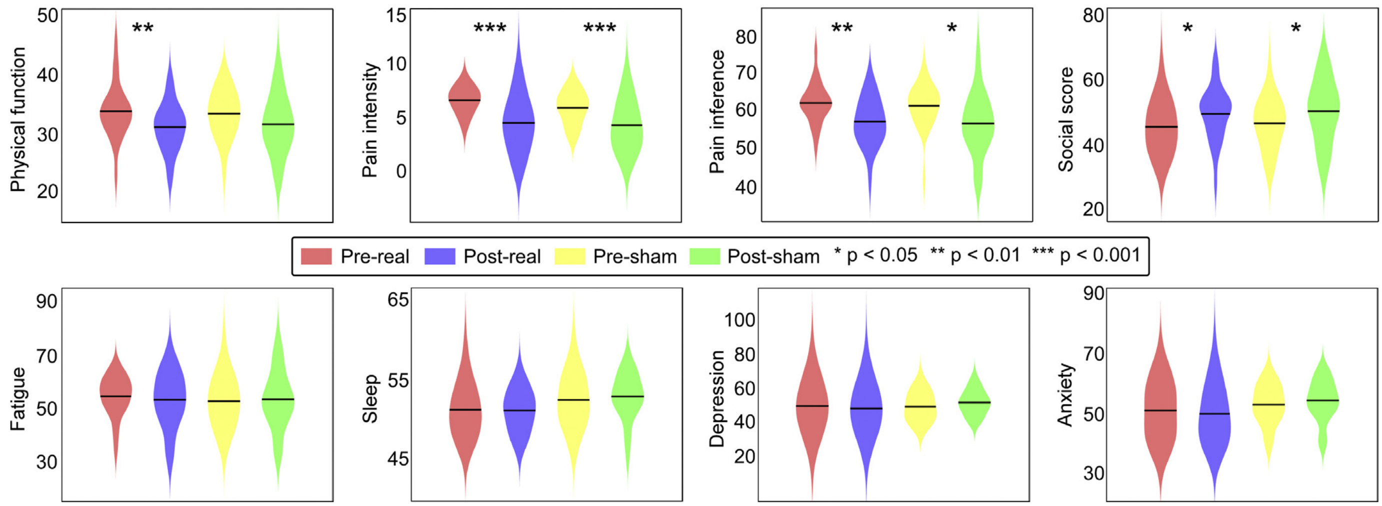

Fig. 4. Pre- and post-treatment clinical subscores of cLBP patients. Real and sham acupuncture significantly improved symptoms in physical function, pain intensity, pain interference, and social scores.

4. Discussion

In this study, we used multivariate resting-state FC within and across four networks (DMN, SN, CEN, and SMN) as features to predict changes in pain severity for both real and sham acupuncture treatment in cLBP patients. We found that real acupuncture produced stronger treatment effects than sham acupuncture, while context manipulation (augmented vs. limited) did not significantly modulate treatment effects. The FCs between the mPFC and the insula, putamen, caudate, and angular gyrus were significantly predictive of real acupuncture treatment responses, while the FCs between the mPFC and dACC, SPL and ParaCL were predictive of sham acupuncture treatment responses. The prediction model accounted for the variability of symptom changes in pain intensity, pain interference, and social scores but was not related to other general symptoms (e.g., depression, anxiety). These results imply that different mechanisms may underlie real and sham acupuncture. Taken together with our recent findings (Tu et al., 2019), the FC between the mPFC and other brain regions in the DMN, SN, CEN, and SMN not only capture the pathophysiology of cLBP, but also have the potential to predict treatment responsiveness.

Neuroimaging studies have shown that cLBP alters brain dynamics beyond the perception of pain (Baliki et al., 2008, 2011). Spontaneous cLBP has a brain representation unique from that of acute pain (Baliki et al., 2011; Tagliazucchi et al., 2010b). Particularly, the mPFC is the primary hub underlying spontaneous pain processing in cLBP (Baliki et al., 2011; Zhang et al., 2019), and mPFC connectivity with the limbic system (e.g., the amygdala and hippocampus) is indicative of pain chronification (Baliki et al., 2012; Hashmi et al., 2013; Vachon-Presseau et al., 2016). In our recent study (Tu et al., 2019), we found abnormal mPFC FC in cLBP patients and investigated its associations with clinical symptoms. Specifically, the baseline FC between the mPFC and the posterior part of the DMN (i.e., the PCC and angular gyrus) was significantly correlated with pain severity. In contrast, we found that the FCs showing significant correlation with changes of pain severity (treatment responses) were mainly between the mPFC and SN (i.e., the insula, putamen, caudate, and dACC). Taken together, these results indicate that while mPFC FC may be indicators for both cLBP pathophysiology and treatment responsiveness, different connectivities and networks (mPFC-DMN and mPFC-SN) were functionally involved.

Recent studies have demonstrated real and placebo treatment differentiated at the brain circuit level (Gollub et al., 2018; Kong et al., 2009a, 2009b; Tétreault et al., 2018; Vachon-Presseau et al., 2018). While the long-term analgesia of real treatment may modulate the development and maintenance of chronic pain with functional and structural brain reorganization, placebo may also alter neural plasticity via a different mechanism. Therefore, it is natural to expect that the baseline predictors of treatment responses for real and sham would be different.

For real acupuncture, we found that connectivity between the mPFC and insula, putamen, and caudate was significantly correlated with treatment responses after 4 weeks of treatment. The insula is a key region integrating the sensory processing system and cognitive modulatory system (Starr et al., 2009), and it has been shown to be activated during acupuncture (Cao et al., 2018; Gollub et al., 2018). In particular, mPFC-insula FC was previously reported to be altered and correlated with symptom changes of knee osteoarthritis patients after acupuncture treatment (Chen et al., 2015). On the other hand, the putamen and caudate are key regions in the dorsal striatum and embedded in distinct cortico-striatal loop circuits, which connect to motor-related cortical areas and frontal association areas. They integrate sensory, cognitive, and affective information to help with decision-making, action selection, and reward seeking (Haruno and Kawato, 2006). We believe that the mPFC-insula FC and mPFC-putamen/caudate FC may reflect patients' unique internal sensory and cognitive states (e.g., reward) for acupuncture treatment, consequently influencing treatment response (Wang et al., 2017).

In contrast, we found that mPFC-dACC connectivity was predictive of treatment response to sham acupuncture. The dACC has been suggested to be involved in the affective but not in the sensory aspect of pain processing, indicating that it supports the motivational and emotional aspects of pain (Lieberman and Eisenberger, 2015). Sham acupuncture, or the placebo effect, has been shown to reduce pain-related negative emotions and consequently improve symptoms of chronic pain (Flaten et al., 2011). Therefore, we speculate that sham acupuncture may reduce symptoms in cLBP patients via the affective pain pathway (medial pain system).

Machine learning models have demonstrated the ability to individualize brain measurements to predict treatment outcomes. For instance, investigators have used machine learning to predict treatment outcomes in patients with depression and anxiety disorders (Doehrmann et al., 2013; Hahn et al., 2015; Whitfield-Gabrieli et al., 2016), schizophrenia (Sarpal et al., 2016) and Parkinson's disease (Ye et al., 2016). The findings from these studies have demonstrated the value and potential of machine learning in the clinical setting. In the present study, we used FC values from baseline to make reliable predictions of clinical symptom changes in response to a longitudinal acupuncture treatment. In addition, unlike other studies predicting treatment responses using initial severity (Doehrmann et al., 2013;

Whitfield-Gabrieli et al., 2016), we found that treatment responses of cLBP patients were not related to their baseline clinical characteristics.

Interestingly, we did not detect significant differences between the high and low context groups, which differs from a previous study showing that a high context group produced greater placebo effects than a low context group (Kaptchuk et al., 2008). In our previous study on knee osteoarthritis patients, we applied a different expectancy manipulation model using heat pain and informed patients that if acupuncture worked on reducing their experience to heat pain, it should also work on their knee pain. We found that this condition-like expectancy method was able to significantly increase the treatment effect after four weeks of knee pain treatment as compared to an identical acupuncture treatment without the expectancy manipulation (Kong et al., 2018). We believe that the failure of verbal + ritual expectancy may mainly be due to individuals' different preferences or characteristics when consulting with doctors (e.g., someone may prefer warm conversations with the doctor, while others may prefer less conversation). Our findings suggest that gaining patients' trust is a complicated process, and warmness and empathy may be just two of several factors that can influence patients' expectancy/belief.

There are several limitations to this study. First, the treatment was only 4 weeks in duration. Thus, the results obtained only represent short- to mid-term effects. Second, our sample size is relatively small, and more studies with larger sample sizes are needed to validate our findings. The cross-validation approach may also lead to unstable and biased estimates when the sample size is small, and the results should be interpreted with caution (Varoquaux et al., 2017). Beyond that, there is a need for validation in a fully independent sample to ensure the robustness of the predictors. Third, participants were allowed to continue their original treatments due to ethical concerns. Thus, the ongoing treatments may be a confounding of our results. However, as a randomized clinical study, we believe that we are largely protected from noise due to other treatments. Further studies with larger sample sizes are needed to further validate our findings.

In conclusion, we demonstrated the ecological feasibility and validity of using multivariate pre-treatment resting-state FCs to predict treatment responses. The present findings provide a quantifiable benchmark for selecting a treatment plan and may facilitate the development of new tools to optimize time, cost, and available resources. Elucidating different FC circuits to predict real and sham acupuncture may shed light on our understanding of mechanisms underlying acupuncture and placebo and may facilitate the development of new methods to enhance acupuncture treatment response (for instance, through brain stimulation methods).

Funding and disclosure

JK is supported by P01 AT006663, R01 AT008563, R61/R33 AT009310, R33AT009341, R21 AT008707 from NIH/NCCIH, and R34DA046635 from NIH/NIDA.

JK has a disclosure to report (holding equity in a startup company, MNT, and pending patents to develop new neuromodulation devices) but declares no conflict of interest. All other authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101885.

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