Relationship between Abnormal Spontaneous Brain Activity and Altered Neuromuscular Activation of Lumbar Paraspinal Muscles in Chronic Low Back Pain

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Research Article

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Abstract

Background

Chronic low back pain (cLBP) affects brain functional activity of the descending pain modulatory network and altered synergistic activation of lumbar paraspinal muscles. However, the neural mechanism underlying functional reorganization and effectiveness of cooperative motion remains unexplored.

Methods

Fifteen cLBP patients and fifteen healthy controls underwent whole brain blood oxygen level-dependent signals measured by functional magnetic resonance imaging technique and amplitude of low-frequency fluctuation (ALFF) analysis method to identify pain-induced changes in regional spontaneous brain activity. A novel approach based on the surface electromyography system and fine-wire electrodes was used to record the EMG signals in the deep multifidus, superficial multifidus and erector spinae.

Results

ALFF was higher in the medial prefrontal cortex, primary somatosensory cortex, motor cortex and inferior temporal cortex in cLBP than at the baseline, whereas lower in the cerebellum, anterior cingulate cortex and posterior cingulate cortex. Further, the decrease in the average electromyography of three lumbar muscles in the cLBP group was positively correlated with the ALFF values of the primary somatosensory cortex, motor cortex, precuneus and middle temporal cortex, but significantly negatively correlated with the medial prefrontal cortex and inferior temporal cortex. Interestingly, the correlation between the functional activity in the cerebellum and the electromyography activity varied in lumbar muscles.

Conclusion

These findings suggest a functional association between abnormal spontaneous brain activity and altered voluntary neuromuscular activation patterns of the lumbar paraspinal muscles, providing new insights into the underlying mechanisms of pain chronicity and important implications for developing novel therapeutic targets of cLBP patients.

1. Introduction

Chronic low back pain (cLBP) is a highly prevalent and recurrent musculoskeletal disease that leads to depression, anxiety and sleep disturbances [1–3]. Previous functional magnetic resonance imaging (fMRI) studies demonstrated that cLBP affects neural activity and alters spatiotemporal dynamics of the blood oxygen level-dependent (BOLD) signals within the large-scale distribution networks associated with sensory, motor, cognitive and affective functions [4–6]. Most neuroimaging observations have shown
abnormal intrinsic activity in the default mode network (DMN) and disrupted functional connectivity of the prefrontal cortex (PFC), cingulate cortex and cerebellum response to nociceptive stimuli [7–9]. Recently, altered functional activation during information encoding and processing was shown to induce inefficient motor control in cLBP [10, 11]. However, the neural mechanism of BOLD activation underlying pain perception and action planning remains unclear.

The amplitude of low-frequency fluctuation (ALFF) is a promising method to detect the regional intensity of spontaneous fluctuations in BOLD signals [12, 13]. Our previous study showed that acute LBP increased ALFF in the medial prefrontal cortex (mPFC), temporal cortex, anterior cingulate cortex (ACC) and cerebellum, but decreased ALFF in the posterior cingulate cortex (PCC)/precuneus and primary somatosensory cortex (S1) [14]. During cLBP, the brain continuously processes signals originating from spontaneous back pain. Chronic pain-induced brain reorganization affects intrinsic functional activity and motion control ability.

The lumbar paraspinal muscles are crucial for posture stabilization, including the lumbar multifidus (LM) and erector spinae (ES) [15–17]. The deep fibers of LM (DM) are vital segmental stabilizers of motion control, whereas the superficial fibers (SM) contribute to spinal compression and extension [18]. Previous surface electromyography (sEMG) studies have shown that DM and SM were differentially activated [19–21]. The timing and amplitude of EMG activity were lower in the DM during cLBP, which potentially reduces its efficacy during functional tasks [22, 23]. No differences were observed between painful and non-painful sides of the DM during maximum isometric back extensions [22]. Contrastingly, the latency of the loading response increased in the SM during self-initiated perturbations [24, 25]. Recent studies have shown that the synergistic activation of LM and lumbar ES was altered in LBP [26]. Altered lumbar neuromuscular control has been implicated in the reoccurrence and chronicity of LBP [27–29]. Therefore, understanding the potential mechanisms can clarify the etiology and pathogenesis of chronic pain, which is essential for developing novel therapies for patients with cLBP.

Here, we aimed to use fMRI and sEMG to investigate the changes in the spontaneous activity of various brain regions and the neuromuscular activation patterns of lumbar muscles in cLBP patients. We examined the mechanism underlying the effect of chronic pain on brain functions and descending nociceptive regulatory system. Specifically, our objectives were: (1) to use fMRI and ALFF to identify the changes in regional spontaneous brain activity during cLBP; and (2) to record the EMG signals of the DM, SM and ES using the sEMG system and fine-wire electrodes to investigate the neuromuscular abnormalities in the lumbar paraspinal muscles; and (3) to explore the potential relationship between the changes in brain function and altered muscle activation in cLBP. We hypothesized that the brain regions involved in sensory, affective and cognitive functions might reflect ALFF changes induced by chronic pain. The altered EMG activity of three lumbar muscles should be evident during cLBP. Furthermore, we investigated the possible association between abnormal spontaneous neural activity and altered muscle activation patterns to facilitate the development of novel therapeutic targets for preventing and treating cLBP.
2. Methods

2.1 Study Design and Ethics Approval

We conducted a case-control study to investigate the changes in the neural activity of regional brain regions and the neuromuscular activity of lumbar muscles during cLBP. We obtained written informed consent from each subject after explaining the detailed instructions on the experimental procedures and the potential risks of the study.

2.2 Subjects

We recruited 15 patients with cLBP (aged 21–57 years), diagnosed by the same physician (M.D.), from the in- and out-patient departments of the First Affiliated Hospital of Sun Yat-sen University. The inclusion criteria consisted of (1) history of cLBP for > 3 months; (2) current pain intensity assessed by the 10-cm visual analog scale (VAS) with a score ranging from 3 to 6; (3) right-handed; and (4) body mass index (BMI) within ± 20% of international standards. Exclusion criteria included: previous history of lumbar spinal surgery, ankylosing spondylitis, severe scoliosis, psychiatric or neurological conditions and psychotropic drug use. We excluded potential female subjects who were pregnant or suffered from dysmenorrhea. The Oswestry Disability Index (ODI) was used to assess pain-related disability.

The control group, consisting of 15 healthy subjects with no pain or drug use (i.e., antipyretics, sleeping pills) within the last month, was recruited after posting notices for on-campus students and staff at the hospital. All subjects were asked to assess unpleasantness using a self-rating anxiety scale (SAS) and self-rating depression scale (SDS). Table 1 shows the group characteristics, indicating similarities in gender, age, educational level, height, weight, BMI, SAS, or SDS scores (P > 0.05).
Table 1
Characteristics of participants (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>cLBP</th>
<th>healthy control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>15</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>7:8</td>
<td>8:7</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.67 ± 11.74</td>
<td>33.60 ± 8.98</td>
<td>0.98</td>
</tr>
<tr>
<td>Education level (years)</td>
<td>15.00 ± 4.24</td>
<td>16.33 ± 2.32</td>
<td>0.30</td>
</tr>
<tr>
<td>H Height (cm)</td>
<td>166.07 ± 7.00</td>
<td>167.00 ± 6.36</td>
<td>0.27</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.20 ± 7.54</td>
<td>59.87 ± 6.15</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>21.41 ± 1.73</td>
<td>21.42 ± 1.05</td>
<td>0.99</td>
</tr>
<tr>
<td>SAS scores</td>
<td>43.50 ± 7.95</td>
<td>31.67 ± 3.86</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SDS scores</td>
<td>48.50 ± 10.59</td>
<td>37.58 ± 7.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Pain intensity (VAS)</td>
<td>4.07 ± 1.03</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Pain duration (years)</td>
<td>4.93 ± 4.34</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>ODI (%)</td>
<td>31.33 ± 17.61</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

cLBP, chronic low back pain; BMI, body mass index; ODI, Oswestry Disability Index; VAS, visual analog scale

2.3 Data Acquisition

The BOLD signals in the whole brain of each subject were measured separately using fMRI scans, while the EMG signals in the lumbar muscles (DM, SM, ES) were measured using sEMG. The measurements were performed in a randomly assigned order and lasted for approximately 20 min.

2.3.1 fMRI data acquisition

MRI data were acquired on a 3-Tesla Siemens Magnetom Prisma scanner (Siemens Healthcare GmbH, Erlangen, Germany) with a standard 8-channel radio-frequency head coil. High-resolution T1-weighted structural images were collected using a fast spin echo sequence (repetition time (TR)/echo time (TE) = 25/3 ms; flip angle = 90°; matrix = 256 × 256). Functional MRI data were acquired using a T2*-weighted single-shot gradient-echo echo-planar imaging sequence (TR/TE = 2000/30 ms; field of view (FOV) = 224 mm × 224 mm; matrix = 64 × 64; flip angle = 90°; 3.5 mm × 3.5 mm in-plane resolution; slice thickness/gap = 3.5/0.7 mm, 33 axial slices, 240 volumes).

2.3.2 EMG data acquisition

The EMG measurement of the lumbar muscle activity was collected using a UMI-sEMG-I system (Umedstrr, Shaoxing, China) with a bandwidth of 15–1000 Hz, resolution of 0.1 µV, common mode
rejection ratio of 110 db and a low noise < 1 µV. Signals from the sEMG system were sampled at 3000 Hz and stored in a computer. Each participant was asked to lie in a prone position on a standard plinth with their head centered on the midline, and the EMG signals from their DM, SM and ES were obtained using the sEMG system and fine-wire electrodes. We removed the insulation of enamel-coated fine-wire (0.16 mm, Friendship Medical Electrodes Company, Xi’an, China) 3 mm from the tip to 20 mm from the end to permit electrical conduction, as mentioned previously. Before testing, compounded lidocaine cream was placed on the planned puncture sites for 5 min to reduce pain during needle insertion.

We placed pairs of recording electrodes of each back muscle with an inter-electrode distance of 0.5–1 cm parallel to the longitudinal rotational axis of the spine, and the reference electrode was placed 4–5 cm lateral to the recording electrodes. Then, four recording fine-wire electrodes consisting of 12-cm wires inside hypodermic needles (25-gauge, 60 mm length) were inserted perpendicularly deep into bilateral DM muscles, which were placed 2 cm lateral to the L4 spinous process on each side. Also, four recording electrodes were inserted 1–2 cm deep into bilateral SM that was 2 cm lateral to the L5/S1 interspinous process. The reference and recording electrodes of the SM consisted of 6-cm wires inside hypodermic needles (24-gauge, 30 mm length), which were inserted into the back muscles. After verifying the location of the recording electrodes using ultrasound (SonoSite M-Turbo, Seattle, USA), the needles were withdrawn, leaving the wire electrodes in the portion of the DM and SM. External fine wires were attached to the skin on each participant’s back using hypoallergenic medical tape, and the bare end of the electrodes was connected to amplifiers using alligator clip electrodes (Qiaotian Technology, Shenzhen, China).

The participants were asked to keep their upper limbs positioned overhead with the elbows flexed to approximately 90° and shoulders abducted to approximately 120°. Then, they were asked to lift their head, trunk and upper extremities with maximum effort, as shown in previous studies assessing the activation of the lumbar muscles in patients with LBP [26, 30]. This measurement was executed thrice with a 30-s rest between movements to elicit the maximum voluntary isometric contraction of the LM for 5 s, and the mean of the three repetitions was calculated for each subject. The cLBP patients were verbally encouraged during the movements.

After collecting the LM data, four recording electrodes detecting the intramuscular EMG activity of the DM were withdrawn approximately 2 cm, leaving the wires in the portion of the bilateral ES (L4 level, ultrasound verified the location). Then participants were asked to perform the same movements as in the LM to obtain the ES’s EMG data.

2.4 Data processing

2.4.1 fMRI data processing

The fMRI image data were preprocessed, and the ALFF was analyzed using the Data Processing Assistant for Resting-State fMRI software (http://rfmri.org/DPARSF) using routines in MATLAB R2013b (MathWorks, Inc., Natick, MA, USA). The BOLD time series preprocessing steps included removal of the
first ten volumes, slice timing correction, motion correction, normalization to the standard echo-planar imaging templates and spatial smoothing with a Gaussian kernel of full-width-half-maximum 4 mm (resampling voxel size = 3 × 3 ×3 mm³). The subjects’ head movements of < 2 mm in translation and 2° in rotation were selected using motion time courses. This data was obtained from all the subjects and used for further analysis. Subsequent analyses included linear trend removal and bandpass filtering (0.01–0.08 Hz) to reduce the effects of very low-frequency drift and high-frequency noise.

The filtered time series were converted into frequency domains with a fast Fourier transform for the ALFF analysis. Since the power of a given frequency is proportional to the square of its amplitude in the original time series in the time domain, the square root was calculated for each frequency of the power spectrum. The averaged square root, obtained across a 0.01–0.08 Hz range at each voxel, represented the ALFF. For standardization, the ALFF of each voxel was divided by the global mean ALFF value.

### 2.4.2 EMG data processing

EMG signals were processed using sEMG analysis-feedback instrument system software V1.0 (Umedstrr, Shaoxing, China), and their features were extracted. The average EMG (AEMG) of the DM, SM and ES were analyzed for each group.

### 2.5 Statistical analysis

Statistical analysis was performed using SPSS 13.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics (mean ± SD) were calculated for age, education, BMI, pain intensity, pain duration, ODI, SAS and SDS scores (data obeyed normal distribution). Random effects in the groups were analyzed using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) to explore the differences in ALFF between cLBP and healthy groups. To extract the ALFF values of the subjects higher than the global mean, one sample t-test was performed against 1 (the global mean ALFF) within each condition. The differences in the ALFF between the two groups were compared using the two-tailed two-sample t-test. We used the REST software (http://rfmri.org/rest) to compare ALFF at each voxel of the whole brain in pain status versus the VAS score.

To analyze the EMG between the groups, we used the mean data for both sides of each group. We used two-sample t-test to determine the potential EMG signal differences for AEMG between cLBP patients and healthy controls to compare the changes in the neuromuscular activation patterns of the DM, SM and ES muscles.

We compared the ALFF at each voxel of the whole brain versus AEMG of DM, SM and ES in cLBP patients using the REST software. The significance of the correlation coefficient was determined using a false discovery rate (FDR) control procedure with a significance level of \( P < 0.05 \) and a minimum cluster size of 10 contiguous voxels.

### 3. Results
All 30 participants included in this study cooperated, and none discontinued participation because of unbearable pain. Therefore, we included the data for each subject in all analyses.

### 3.1 Analyzing ALFF within groups

Figure 1 shows the mean ALFF maps within each group. Upon visual inspection, the PFC showed significantly higher ALFF than the global mean but with different strengths between the two groups ($P<0.05$, FDR, cluster size $\geq 10$).

### 3.2 Analyzing ALFF between groups

The group analysis showed significant differences in ALFF between cLBP patients and healthy control (Fig. 2, Table 2). Compared with the baseline level, cLBP patients showed increased ALFF in the bilateral mPFC, right S1, right motor cortex (M1) and left inferior temporal cortex (ITC), but decreased ALFF in bilateral cerebellum, bilateral ACC and left PCC.

<table>
<thead>
<tr>
<th>Brain region BA Cluster sizes</th>
<th>Peak t-value</th>
<th>Peak MNI coordinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/R medial prefrontal cortex</td>
<td>10/9 27/24</td>
<td>7.05/6.51 -3/6 21/-21 -18/21</td>
</tr>
<tr>
<td>R primary somatosensory cortex</td>
<td>20</td>
<td>7.10 33/33 48</td>
</tr>
<tr>
<td>R motor cortex</td>
<td>4 22</td>
<td>6.40 42/24 63</td>
</tr>
<tr>
<td>L inferior temporal cortex</td>
<td>37 10</td>
<td>5.92 -42/48 -18</td>
</tr>
<tr>
<td>L/R cerebellum</td>
<td>- 72/54</td>
<td>-6.85/-7.77 -15/15 -51/-66 -36/-24</td>
</tr>
<tr>
<td>L/R anterior cingulate cortex</td>
<td>24/24 57/17</td>
<td>-7.25/-7.02 -6/9 22/30 26/9</td>
</tr>
<tr>
<td>L posterior cingulate cortex</td>
<td>23 78</td>
<td>-7.45 -3/-33 21</td>
</tr>
</tbody>
</table>

*two-sample t-test analysis, $P<0.05$ (FDR), $K \geq 10$.*

**Abbreviations:** BA = Brodmann Area, MNI = Montreal Neurological Institute; L = Left, R = Right

### 3.3 Correlations between ALFF and VAS scores

Correlation analysis revealed a strong positive association between ALFF in the right mPFC and VAS scores.

### 3.4 Analyzing the EMG activity between groups

We found that the AEMG signals recorded from the DM, SM and ES muscles of the cLBP group were lower than in the healthy control group ($P<0.01$, Table 3).
Table 3
Between-group analyses of EMG activity (AEMG) in the lumbar muscles

<table>
<thead>
<tr>
<th>cLBP</th>
<th>healthy control</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>216.40 ± 53.63</td>
<td>379.08 ± 82.41</td>
<td>-6.408</td>
</tr>
<tr>
<td>SM</td>
<td>75.00 ± 31.70</td>
<td>112.48 ± 28.59</td>
<td>-3.401</td>
</tr>
<tr>
<td>ES</td>
<td>98.44 ± 26.58</td>
<td>165.05 ± 31.79</td>
<td>-6.226</td>
</tr>
</tbody>
</table>

AEMG, average EMG; cLBP, chronic low back pain; DM, deep multifidus; SM, superficial multifidus; erector spinae, ES

3.5 Correlations between ALFF and EMG activity

The AEMG of DM, SM and ES in the cLBP group was positively correlated with the ALFF in the S1, M1, precuneus and middle temporal cortex (MTC), but significantly negatively correlated with mPFC and ITC (Fig. 3, Table 4). Moreover, the ALFF in the cerebellum showed significant positive correlations with the AEMG of the DM, negative correlations with the AEMG of the SM, and no correlation with the AEMG of the ES in cLBP patients. Correlation analysis also indicated a strong positive association between ALFF in the ACC and the AEMG of the DM. Still, no significant association was found between ALFF in this region and AEMG of the SM or the ES.
<table>
<thead>
<tr>
<th>Lumbar muscle</th>
<th>Brain region</th>
<th>BA</th>
<th>Cluster sizes</th>
<th>Peak r-value</th>
<th>Peak MNI coordinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>R primary somatosensory cortex</td>
<td>2</td>
<td>17</td>
<td>0.86</td>
<td>18 -48 60</td>
</tr>
<tr>
<td></td>
<td>R motor cortex</td>
<td>4</td>
<td>43</td>
<td>0.82</td>
<td>3 -21 78</td>
</tr>
<tr>
<td></td>
<td>L precuneus</td>
<td>7</td>
<td>19</td>
<td>0.82</td>
<td>-21 -87 39</td>
</tr>
<tr>
<td></td>
<td>L middle temporal cortex</td>
<td>39</td>
<td>12</td>
<td>0.83</td>
<td>-48 -66 21</td>
</tr>
<tr>
<td></td>
<td>R cerebellum</td>
<td>–</td>
<td>12</td>
<td>0.93</td>
<td>51 -48 -33</td>
</tr>
<tr>
<td></td>
<td>L anterior cingulate cortex</td>
<td>32</td>
<td>15</td>
<td>0.81</td>
<td>-12 15 42</td>
</tr>
<tr>
<td></td>
<td>L/R medial prefrontal cortex</td>
<td>9</td>
<td>19/12</td>
<td>-0.85/-0.82</td>
<td>-48/27 27/9 24/42</td>
</tr>
<tr>
<td></td>
<td>R inferior temporal cortex</td>
<td>20</td>
<td>22</td>
<td>-0.82</td>
<td>66 -24 -21</td>
</tr>
<tr>
<td></td>
<td>SM R primary somatosensory cortex</td>
<td>3</td>
<td>17</td>
<td>0.88</td>
<td>54 -9 24</td>
</tr>
<tr>
<td></td>
<td>R motor cortex</td>
<td>4</td>
<td>24</td>
<td>0.91</td>
<td>30 -27 66</td>
</tr>
<tr>
<td></td>
<td>L/R precuneus</td>
<td>19/19</td>
<td>23/11</td>
<td>0.82/0.84</td>
<td>-21/36 -81/-81 39/36</td>
</tr>
<tr>
<td></td>
<td>L middle temporal cortex</td>
<td>39</td>
<td>36</td>
<td>0.90</td>
<td>-45 -60 15</td>
</tr>
<tr>
<td></td>
<td>L medial prefrontal cortex</td>
<td>9</td>
<td>20</td>
<td>-0.84</td>
<td>-54 15 36</td>
</tr>
<tr>
<td></td>
<td>L/R cerebellum</td>
<td>–/–</td>
<td>15/18</td>
<td>-0.92/-0.83</td>
<td>-12/9 -57/-54 -45/-45</td>
</tr>
<tr>
<td></td>
<td>R inferior temporal cortex</td>
<td>20</td>
<td>13</td>
<td>-0.86</td>
<td>66 -24 -21</td>
</tr>
<tr>
<td></td>
<td>ES R primary somatosensory cortex</td>
<td>3</td>
<td>18</td>
<td>0.83</td>
<td>60 -9 21</td>
</tr>
<tr>
<td></td>
<td>R motor cortex</td>
<td>4</td>
<td>40</td>
<td>0.85</td>
<td>33 -27 66</td>
</tr>
<tr>
<td></td>
<td>L/R precuneus</td>
<td>19/19</td>
<td>17/11</td>
<td>0.88/0.83</td>
<td>-18/27 -81/-75 36/33</td>
</tr>
<tr>
<td></td>
<td>R middle temporal cortex</td>
<td>39</td>
<td>19</td>
<td>0.81</td>
<td>48 -57 3</td>
</tr>
<tr>
<td></td>
<td>L medial prefrontal cortex</td>
<td>9</td>
<td>30</td>
<td>-0.85</td>
<td>-54 15 36</td>
</tr>
<tr>
<td></td>
<td>R inferior temporal cortex</td>
<td>20</td>
<td>11</td>
<td>-0.81</td>
<td>66 -24 -21</td>
</tr>
</tbody>
</table>

Correlation analysis, $P<0.05$ (FDR), $K \geq 10$.

Abbreviations: BA = Brodmann Area, MNI = Montreal Neurological Institute; L = Left, R = Right; AEMG, average EMG.

### 4. Discussion
Here, we explored the function-activity relationships of hemodynamic and EMG signals in cLBP patients and healthy subjects. Our results revealed that chronic pain evoked significant differences in the DMN, salience network, sensorimotor cortices and cerebellum. Also, the AEMG of the cLBP group was significantly decreased in the DM, SM and ES. Moreover, AEMG of lumbar paraspinal muscles was positively correlated with ALFF changes in the S1, M1, precuneus and MTC, but significantly negatively correlated with the mPFC and ITC in cLBP. Notably, functional activity recorded from the cerebellum was differentially correlated with EMG activity in the DM, SM and ES.

Consistent with previous research reporting changes in neuromuscular activation of LM and ES in response to chronic pain [10, 15], our findings showed that AEMG was significantly lower in cLBP patients than the pain-free controls. The data suggested altered trunk muscle recruitment and reduced effectiveness of co-contraction during functional tasks related to persistent nociceptive stimulation [31]. These findings also support the hypothesis that pain alters spinal motor control patterns, causing a redistribution of activation within the back muscles [29, 32]. cLBP impacts multiple neural networks and descending pathways that control the lumbar muscles [33]. However, the mechanism underlying the decline in postural control influenced by brain functional plasticity in cLBP needs to be explored further.

Recent brain fMRI studies confirmed that the DMN is disrupted in acute and chronic pain [34–36]. This study reported ALFF changes in the PCC/precuneus, mPFC and parietal cortex, implying that chronic pain evokes abnormal DMN activity and alterations in neural systems for episodic memory and executive processing [37–40]. Moreover, this network can modulate the perception of chronic noxious stimuli through other antinociceptive descending modulation networks [41], indicating that the development and recurrence of cLBP might be initiated by the functional alterations in the DMN. PCC/precuneus, a critical node within the circuitry, showed significantly lower ALFF in cLBP. The ALFF changes in the precuneus also had significant positive correlations with lumbar muscle activation (DM, SM, ES) changes, suggesting that pain stimuli might induce decreased functional activity and impaired posture control. The mPFC is critical for the responses to modulation, expectancy and emotional processing [6, 14]. Recent functional imaging studies suggest that the mPFC shows a higher correlation than other areas on various tasks [6, 14]. This study revealed significant ALFF increases in the bilateral mPFC following sustained pain stimuli. Particularly, the greater intrinsic activity of this region was strongly correlated with pain intensity. Moreover, a significant negative association was found between ALFF changes in the mPFC and decreased AEMG of the DM, SM, ES during cLBP. These findings prove that chronic pain alters DMN dynamics, leading to lower coordination and execution ability, which might further alter neuromuscular activation patterns of back muscles.

As a central component of the salience network, ACC is associated with pain perception and responds directly to noxious stimuli [42]. The regional cerebral blood flow is decreased in the bilateral ACC in cLBP, demonstrating that ACC deactivation might cause inefficient pain processing or compensatory damage in functionally relevant regions, such as the PFC [43]. Moreover, ACC is responsible for encoding the affective dimensions of pain perception, disrupted activity in this region might reflect a negative emotional response and serve to modulate mesocorticolimbic activity [44]. Although our research mainly
focuses on young and middle-aged subjects, we observed an apparent trend in the differences between unpleasantness (i.e., depression, anxiety) in pain group. Furthermore, pain-related fear is directly associated with reduced lumbar flexion and altered EMG activity of the lumbar muscles in cLBP [45]. Notably, we found that ALFF was decreased in the left ACC with a decreased neuromuscular function of the DM, indicating that with the development of neuromuscular activation abnormalities and coordination impairments, the lower spontaneous neural activity changes in this region. The data further support the idea that the inhibitory system contributes to the pathogenic mechanism of cLBP.

We demonstrated significant increases ALFF in the right S1 and right M1 during cLBP and proved that changes in sensorimotor cortices reflect alterations in the perception of noxious signals. However, the changes in the BOLD signals of the sensorimotor cortices positively correlated with EMG signals of the lumbar muscles (DM, SM, ES). We confirmed a trend that the decrease in ALFF value was correlated with a reduction in AEMG during chronic pain, suggesting that the inhibition of sensorimotor cortices might represent maladaptive movement and motor control impairments that further affect delayed activation of core stability back muscles. In addition, decreased lumbar spine stability degrades the functional organization of sensorimotor cortices and attenuates responses to peripheral nociceptive stimuli, exacerbating pathological changes. Pain stimuli evoked opposing stimulus-response results, this might be because most of the cLBP patients were young and middle-aged adults, increased corticomotor excitability might be a beneficial short-term adaptation with a significantly increased nociceptive signaling. As the slow rate of neuromuscular activation contributed to back muscle dysfunction, chronic progressive conditions gradually caused “decompensation” and demonstrated lower spontaneous activity in the S1 and M1 associated with higher sustained pain [46].

Previous studies showed positive changes in the BOLD signal and altered spontaneous brain activity in the ITC during pain sensation [14, 47]. Additionally, the ALFF value had significant negative correlations with AEMG changes in the lumbar paraspinal muscles (DM, SM, ES) in the cLBP group. Therefore, cLBP patients exhibited lower EMG activity but higher ALFF in the ITC than that at baseline. This shows that chronic pain alters motor control patterns of trunk stabilizing muscles, enhancing recognition memory and behavioral responses [47]. Correlation analysis also showed that changes in spontaneous neural activity in the MTC had a significant positive correlation with the alterations in the neuromuscular signals of the DM, SM and ES, implying that MTC deactivation might be involved in maladaptive movement and pain modulation impairments resulting from persistent afferent nociception [27, 48].

Cerebellar function is important in LBP because the pain-specific region directly receives afferent input from peripheral nociceptive pathways and is involved in cognitive processing [49]. Unlike the activated dynamics seen in the cerebellum during acute LBP, ALFF in the cerebellum significantly decreased with chronic pain. Interestingly, ALFF changes in the cerebellum showed significant positive correlations with AEMG changes in the DM, but negative correlations with AEMG changes in the SM, indicating that the DM and SM were differentially activated [50, 51]. The amplitude correlation is important because it indicates the importance of DM in neuromuscular function to control the motion segment of human spinal system. The cortical excitability of the cerebellum decreased with the development of DM dysfunction.
Contrastingly, the correlation between decreased EMG in the ES and functional alterations of the cerebellum was insignificant. Therefore, we suggest that the changes in the timing of ES activation might not affect the cerebellum function.

In conclusion, we revealed a functional relationship between abnormal spontaneous neural activity in various brain regions and pain-induced neuromuscular alterations in the lumbar paraspinal muscles. The BOLD activations mainly occurred in the mPFC, S1, M1 and ITC, while deactivations occurred in the PCC/precuneus, cerebellum and ACC, which was highly correlated with the EMG measurements in the cLBP group. Interestingly, we showed a differential correlation between the EMG signals of the deep and superficial LM corresponding to pain-related changes with the BOLD signals in the cerebellum. These findings suggest that cLBP altered functional activation during information encoding and emotional processing, causing inefficient executive cognitive control and motor coordination impairment. Our findings support the idea that altered brain functional networks reflect top-down control over pain and cognitive reappraisal of pain. Improving the functional activity of specific brain regions involved in sensory, affective and cognitive functions might provide a novel intervention target for preventing and treating cLBP [52, 53]. Future research should focus on the brain’s functional plasticity during rehabilitation therapy and develop non-invasive neuromodulation techniques for cLBP to reduce secondary hyperalgesia and enhance activation of the descending pain modulatory network.

**Abbreviations**

cLBP  chronic low back pain

fMRI  functional magnetic resonance imaging

BOLD  blood oxygen level-dependent

ALFF  amplitude of low-frequency fluctuation

DMN  default mode network

mPFC  medial prefrontal cortex

ACC  anterior cingulate cortex

PCC  posterior cingulate cortex

S1  primary somatosensory cortex

M1  motor cortex

ITC  inferior temporal cortex

MTC  middle temporal cortex
DM  deep multifidus
SM  superficial multifidus
ES  erector spinae
sEMG  surface electromyography
VAS  visual analog scale
ODI  Oswestry Disability Index
SAS  self-rating anxiety scale
SDS  self-rating depression scale

Declarations

Author contributions

SZ designed and conducted the experiment, performed the analysis and wrote the manuscript. YW conducted the experiment and performed the analysis. TL contributed to conception and design of the study. JM made contribution for the interpretation of data. RH conducted the experiment of magnetic resonance imaging data. XH guided the development of the project protocol and advised on ethical considerations. WW designed and conducted the experiment and was involved in revising the manuscript. CW made contribution to conception and design, interpretation of data, and revising the manuscript.

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Availability of data and materials

All datasets generated including usability observation forms and statistical calculations are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was granted by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University. The reference code was: ([2017]250). All participants signed a consent form with reference to
a detailed participant information sheet. They were made aware of their right to withdraw from the study without need for explanation or any impact on future services or opportunities.

**Consent for publication**

All authors gave consent for the publication.

**Competing interests**

No conflicts are to be declared by the authors.

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Figures
Mean ALFF maps in healthy subjects and cLBP patients ($P < 0.05$, cluster threshold $\geq 10$). Abbreviations: ALFF, amplitude of low-frequency fluctuation; cLBP, chronic low back pain.
Resting-state ALFF differences between cLBP and baseline ($P < 0.05$, cluster threshold $\geq 10$). Compared with the baseline level, cLBP showed higher ALFF in the bilateral medial prefrontal cortex, right primary somatosensory cortex, the right motor cortex and the left inferior temporal cortex. Conversely, lower ALFF was seen in the bilateral cerebellum, bilateral ACC, and left PCC under pain stimuli. Note: On the color bar (lower section), reddish-yellow and bluish-green colors indicate the status-averaged increases and decreases. Abbreviations: ALFF, amplitude of low-frequency fluctuation;cLBP, chronic low back pain.
Figure 3

Correlations between ALFF and AEMG in cLBP ($P < 0.05$, cluster threshold $\geq 10$). AEMG of the lumbar paraspinal muscles (DM, SM, ES) in the cLBP group was positively correlated with ALFF in the sensorimotor cortices, precuneus and MTC, but significantly negatively correlated with mPFC and ITC. The ALFF of the peak voxel in the cerebellum had significant positive and negative correlations with the AEMG of the DM and SM, respectively. It was not correlated with the AEMG of the ES in LBP. The left-hand side of the figure corresponds to the right side of the brain. Abbreviations: ALFF, amplitude of low-frequency fluctuation; AEMG, average EMG; cLBP, chronic low back pain; DM, deep multifidus; SM, superficial multifidus; erector spinae, ES; mPFC, medial prefrontal cortex; MTC, medial prefrontal cortex; ITC, inferior temporal cortex.