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ORIGINAL ARTICLE

# Attenuation of cortical activity triggering descending pain inhibition in chronic low back pain patients: a functional magnetic resonance imaging study

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**Abstract**
*Purpose* A considerable portion of chronic low back pain (cLBP) patients lack anatomical abnormality, resist conventional therapeutic interventions, and their symptoms are often complicated with psychological and social factors. Such patients have been reported to show cerebral abnormalities both in anatomy and function by neuroimaging studies. Here we examined differences in cerebral reactivity to a simulated low back pain stimulus between cLBP patients and healthy controls by functional magnetic resonance imaging (fMRI), and their behavioral correlates from a psychophysical questionnaire.
*Methods* Eleven cLBP patients and 13 healthy subjects (HS) were enrolled in this study. After psychophysical evaluation on-going pain with McGill Pain Questionnaire Short Form (MPQ), they underwent whole-brain fMRI in a 3-Tesla MRI scanner while receiving three blocks of 30-s mechanical pain stimuli at the left low back with a 30-s rest in between, followed by a three-dimensional anatomical imaging. Functional images were analyzed with a multi-subject general linear model for blood oxygenation level-dependent (BOLD) signal changes associated with pain. Individual BOLD signal amplitudes at activated clusters were examined for correlation with psychophysical variables. Two in the cLBP and five data sets in the HS groups were excluded from analysis because of deficient or artifactual data or mismatch in age.
*Results* The HS group showed LBP-related activation at the right insular cortex, right dorsolateral prefrontal cortex (DLPFC), left anterior cingulate cortex (ACC), and left precuneus; and deactivation in a large area over the parietal and occipital cortices, including the bilateral superior parietal cortex. On the other hand, the cLBP group did not show any significant activation at those cortical areas, but showed similar deactivation at the bilateral superior parietal cortex and part of the premotor area. An HS > cLBP contrast revealed significantly less activity at the ACC and DLPFC in the cLBP group, which was negatively correlated with higher MPQ scores.
*Conclusions* The cLBP patients showed attenuated reactivity to pain at the ACC and DLPFC, known cortical areas mediating affective component, and top-down modulation, of pain. The present results might be associated with possible dysfunction of the descending pain inhibitory system in patients with chronic low back pain, which might possibly play a role in chronification of pain.

**Keywords** Chronic low back pain · Functional magnetic resonance imaging · Descending pain inhibitory system · Anterior cingulate cortex · Dorsolateral prefrontal cortex

## Introduction

Seventy to 80% of adults experience low back pain at least once in a lifetime [1, 2]. Although 90% of them get relieved of pain within 12 weeks [2], the rest continue to suffer from chronic low back pain (cLBP) without any definitive signs of anatomical abnormalities in the spine, peripheral nerves, or the musculoskeletal system. A clinical profile of cLBP

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often involves psychosocial factors as well as physical disability. Psychological distress and depressive mood play major roles in the transition from acute LBP to cLBP [3].

Patients with cLBP also show anatomical and functional alterations in the brain. Gray matter density was found decreased at the dorsolateral prefrontal cortex and the thalamus by voxel-based morphometry in cLBP patients [4]. Cerebral functional changes have also been pursued by a conventional functional magnetic resonance imaging (fMRI) technique based on blood oxygenation level-dependent (BOLD) contrast. cLBP patients were found to show higher intensity of pain perception as well as larger activations at the pain-related brain areas in response to pressure-induced pain at the other body parts than lower back [5]. Kobayashi et al. also noted that cLBP patients showed higher unpleasantness of pain as well as more pronounced activation at the posterior cingulate cortex during pressure stimulus-induced simulated low back pain than healthy controls [6]. Overall, those neuroimaging results also implicate possible plastic, functional changes in the brain that might play some roles in sensory, emotional, and cognitive abnormalities in cLBP patients.

On the other hand, chronic pain was associated with decreased connectivity of the default mode network [7], which is known to show negative activation commonly by diverse salient tasks/stimuli and to play important roles in core cognitive functions and internal awareness [8]. Such phenomenon might implicate a possible modification of cerebral top-down, inhibitory mechanisms [9] in cLBP patients.

In the present study, we specifically aimed to examine the details of such inhibitory mechanisms possibly modified in cLBP patients. We used fMRI with simulated LBP stimulation and sought for negative as well as positive activations by pain. We tested a hypothesis that cLBP patients might show a decreased negativity of the default mode network during pain, and also a modified top-down component of pain-related activation. We also examined possible associations among various psychophysical variables and pain-related brain activities.

## Subjects and methods

The present study was approved by the ethics review board of Fukushima Medical University (IRB No. 899) and was conducted in compliance with ethical standards by the Declaration of Helsinki [10]. It was performed at a hospital (Southern Tohoku General Hospital) affiliated with Fukushima Medical University from 2009 to 2011. We recruited candidate patients and subjects at our outpatient care clinics and by advertisement.

### Subjects

Eleven cLBP patients (nine males, two females) and 13 healthy subjects (HS; 13 males) were enrolled. Written informed consent was obtained from all subjects. They were all right-handed, had no history of cerebrovascular disease, and were free from any medications within 24 h before an experiment. Exclusion criteria included any structural abnormalities in the lumbar spine on MRI and any other specific neurologic symptoms.

Using an 11-point numerical rating scale of pain intensity (NRS-i), cLBP was defined as low back pain lasting longer than 3 months with an NRS-i score of 3 or more. NRS-i "0" indicates the absence of pain, "1" slight pain, and "10" the highest imaginable degree of pain. McGill Pain Questionnaire Short Form (MPQ) was used to evaluate overall severity of pain calculated from both sensory and affective components of pain [11].

Subjects in the HS group had never experienced LBP lasting longer than 1 week. Efforts were made to match age and sex between the cLBP and HS groups. Required sample sizes were determined as between 8 and 10 for each group based on our previous study [6] that attained sufficient statistical robustness for behavioral and imaging data analysis.

### Pain stimulation

Similarly to the method reported by Kobayashi [6], an algometer was custom-made from an empty disposable 25-ml syringe with its head sealed and rounded. Briefly, with the rubber-cushioned tail of the pusher orthogonally placed on the target of stimulation, manual compression on the sheath caused displacement of the pusher, (displacement was gauged by the printed scale on the side of the sheath) and a pressure stimulus on the tail. The pressure stimulus was calculated from the distance of the displacement and semi-quantified in kilopascals. The surface of the tail was approximately 3 $cm^2$.

### Experimental paradigm

During MRI acquisition, each subject was placed in the prone position in order to receive a mechanical pressure stimulus at the lumbar region. The subject's head was immobilized using a custom-made Styrofoam mask to minimize head motion during imaging. The tail of the algometer was placed orthogonally on the intercrestal line (the Jacoby line), 5 cm to the left of the median line on the lower back. A mechanical stimulus was given by pushing the sheath of the syringe downward on the lower back. The intensity of pain stimulus was determined from the distance of sheath displacement measured with a scale marked

on the syringe. Time to peak of the pressure stimulus was approximately 2 s.

Each subject underwent whole-brain fMRI while receiving a blocked-design pain stimulation paradigm, which consisted of three blocks of 30-s painful stimulus at 500 kPa with 30 s of intervening rest conditions. During imaging, the subject was asked to remember the level of pain intensity and unpleasantness caused by each of the three lumbar mechanical stimuli. Pain intensity and unpleasantness were evaluated after each session. As well as NRS-i, the NRS of unpleasantness (NRS-u) was assessed in 11 points (0–10) with "0" indicating no unpleasantness, "1" slight unpleasantness, and "10" the highest imaginable degree of unpleasantness.

### MRI scanner and pulse sequences

A 3.0-Tesla MRI scanner (Signa®, GE Healthcare, Milwaukee, MI, USA) was used, and fMRI was performed under the following parameters: repetition time, 3000 ms; echo time, 50 ms; flip angle, 90°; field of view, 240 mm; matrix, 64 × 64; interslice time, 120 ms; number of slices, 25; slice thickness, 4 mm; gap, 1 mm; and voxel size, 3.75 × 3.75 × 4 mm. Furthermore, a three-dimensional high-resolution anatomic image was acquired, with a fast spoiled gradient-recalled acquisition at steady-state sequence, to be registered with functional images under the following parameters: repetition time, 650 ms; echo time, minimum-full; flip angle, 10°; field of view, 240 mm; matrix, 256 × 256; slice thickness, 1.4 mm; no slice gap; and 120 axial slices.

### Analysis

Demographic and psychophysical parameters were statistically compared between the cLBP and HS groups using an unpaired $t$ or Fisher's exact test where appropriate, and $p < 0.05$ was considered statistically significant.

Functional images were preprocessed using BrainVoyager QX® software (Brain Innovation, Maastricht, The Netherlands) and the effects of head motion were corrected. Signal time courses of pain-related cerebral activation or deactivation were examined at the peak voxel of each cluster. Briefly, the functional images of the cLBP patients and HS were analyzed using a multi-subject general linear model analysis. A block design stimulation paradigm was convoluted with a two-gamma hemodynamic response function and time to response peak of 5 s. Group-based (HS, cLBP) and contrast (HS > cLBP) maps were generated using a fixed-effects analysis with a false discovery rate at $p < 0.05$. To remove false positive activation in areas with high inhomogeneity of magnetic fields, we excluded voxels with arbitrary signal intensity < 1000, set a cluster threshold at 300 voxels, and smoothed images at a full-width half-maximum of 3 voxels. Correlations were sought between the maximal percent changes of the BOLD signals of activated/deactivated clusters, and each of the psychophysical parameters obtained with pre-scan or between-scan questionnaires. Stereotaxic coordinates of areas with cerebral activation were determined using the atlas by Talairach and Tournoux [12].

## Results

### Subject demographics

We excluded two cLBP and five HS data sets from analysis for the following reasons: one cLBP and tree HS fMRI data sets were contaminated by significant artifacts from head motion, larger than half a voxel size, or scanner noise; one cLBP data lacked psychophysical parameters; and two HS data did not match in age. We therefore used data sets from nine cLBP patients (eight male and one female) and eight healthy subjects (eight males) for all the following analysis, which were within the required sample sizes as stated above.

The ages of subjects were 48 ± 14.0 (mean ± SD; range, 25–66) years in the cLBP group and 34 ± 13.9 (25–61) years in the HS group. There were no significant differences in age ($p = 0.057$) and sex ($p = 0.33$) between the groups.

### Pain intensity and unpleasantness

With the 500-kPa pain stimulation, the NRS-i scores were 6.1 ± 2.2 and 6.0 ± 1.1, in the cLBP and HS groups, respectively. The NRS-u scores in the cLBP and HS groups were 5.9 ± 2.9 and 5.0 ± 1.9, respectively. The intensity of pain and unpleasantness did not differ significantly between the groups.

### Low back pain-related cerebral activation

In the HS group, we observed low back pain-related activation at the right insular cortex (IC), right dorsolateral prefrontal cortex (DLPFC), left anterior cingulate cortex (ACC), and left precuneus, and deactivation at a large area spanning the parietal and occipital cortices including the bilateral superior parietal cortex (Table 1; Figs. 1, 2).

In the cLBP group, we did not observe any significant activation, but found similar deactivation in the bilateral superior parietal cortex as well as at the premotor area (Table 1; Fig. 3).

**Table 1** Brain areas activated by mechanical lumbar stimulation at 500 kPa

| Region of activation | Talairach coordinates | | | | |
|---|---|---|---|---|---|
| | *x* | *y* | *z* | *t* | Cluster size |
| Healthy subjects (HS, $n = 8$) | | | | | |
| R Insular cortex (BA13) | 32 | 10 | 15 | 4.12 | 4632 |
| L anterior cingulate cortex (BA32) | −1 | 22 | 45 | 3.45 | 2997 |
| L anterior cingulate cortex (BA24) | −1 | 1 | 45 | 2.96 | 453 |
| R dorsolateral prefrontal cortex (BA9) | 35 | 22 | 36 | 2.82 | 372 |
| L precuneus (BA30) | −4 | −68 | 12 | 3.00 | 343 |
| L superior parietal cortex (BA31) | −28 | −71 | 18 | −4.62 | 31882 |
| R superior parietal cortex (BA31) | 14 | −56 | 21 | −3.72 | 8791 |
| Chronic low back pain patients (cLBP, $n = 9$) | | | | | |
| L superior parietal cortex (BA40) | −37 | −56 | 18 | −4.65 | 44907 |
| R superior parietal cortex (BA31) | 23 | −32 | 36 | −4.11 | 21463 |
| L premotor area (BA6) | −19 | 13 | 54 | −3.02 | 361 |
| Contrast (HS–cLBP) | | | | | |
| L anterior cingulate cortex (BA24) | −7 | −17 | 39 | 3.40 | 316 |
| L dorsolateral prefrontal cortex (BA8) | −25 | 16 | 39 | 3.43 | 1164 |

Three-dimensional Talairach coordinates are indicated for each significant cluster with the maximum *t* value and cluster size in $mm^3$

*R* right, *L* left, *BA* Brodmann area

An HS-cLBP contrast map revealed two positive clusters; the left ACC [Brodmann's area (BA) 32] and left DLPFC (BA 8) (Table 1; Fig. 4).

### Signal time-course analysis of regions of interest

Although the clusters at the ACC and DLPFC showed positive BOLD signals in the HS group (Fig. 2), they showed negative BOLD signals in the cLBP group at both of those areas (Fig. 5). On the other hand, the clusters at the superior parietal lobule showed significant deactivation in both the HS and cLBP groups, followed by a post-stimulus positive overshoot (Fig. 6). The peak BOLD amplitudes in the right superior parietal lobule were slightly larger in the cLBP group than that in the HS group, although not statistically significant (Fig. 6).

### Correlation analysis between the psychophysical parameters and the %BOLD signal changes

The BOLD signal changes at the left DLPFC and ACC were negatively correlated with the total MPQ scores in the cLBP group (Fig. 7). The determination coefficients between the %BOLD signal changes and MPQ scores were $R^2 = 0.53$ ($r = -0.73$, $p < 0.05$) and $R^2 = 0.32$ ($r = -0.56$, $p < 0.05$), respectively, at the DLPFC and ACC. On the other hand, we did not find any statistically significant correlations between those BOLD signal changes and any of the other behavioral variables including NRS-i, NRS-u, sensory, and affective MPQ scores.

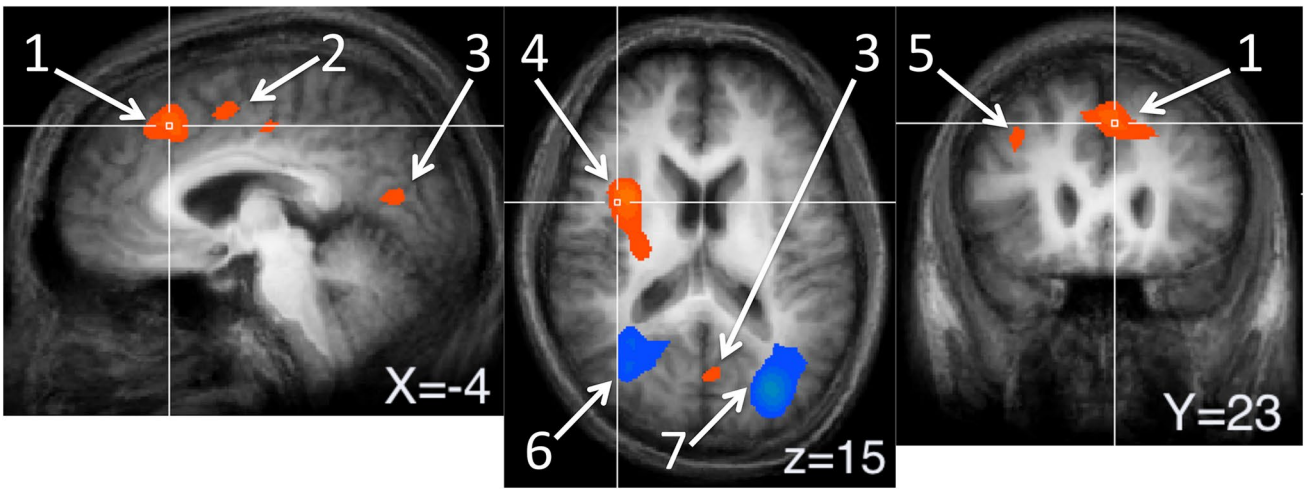


**Fig. 1** Cerebral activation by mechanical pain stimulation in the HS group. Cerebral activation and deactivation was observed under mechanical pain stimulation at 500 kPa at the lower back. *1* Left anterior cingulate cortex (ACC; BA32), *2* left ACC (BA24), *3* left precuneus, *4* right insular cortex, *5* right dorsolateral prefrontal cortex, *6* right superior parietal cortex, *7* left superior parietal cortex. *Red* or *yellow* indicates activated areas. *Green* or *blue* indicates deactivation. *BA* Brodmann area

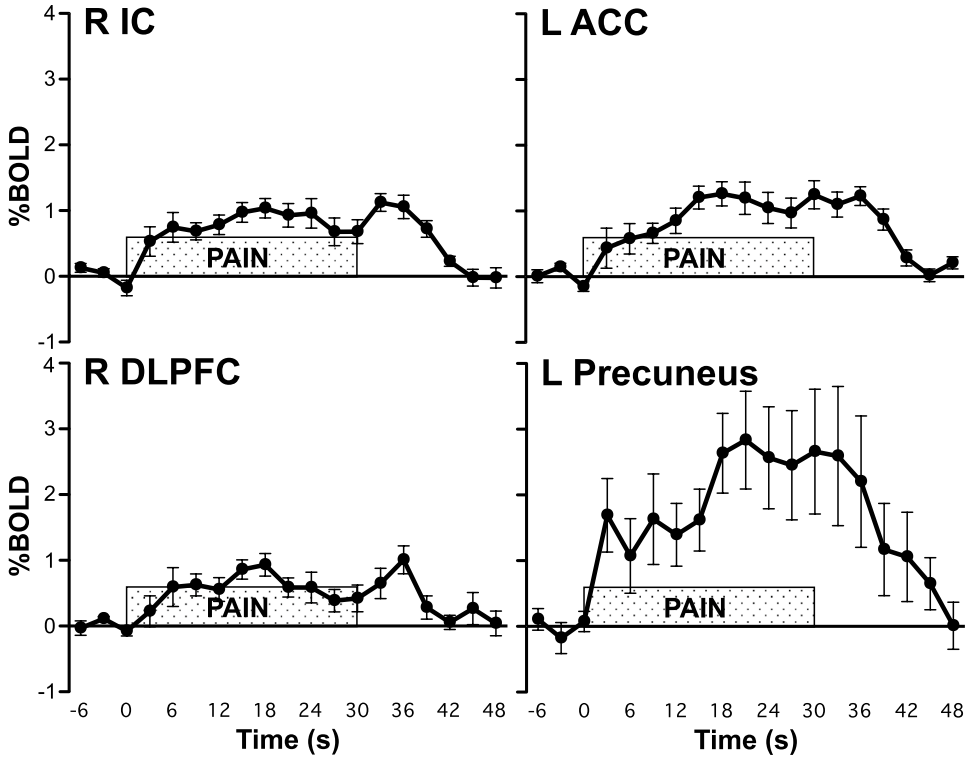


**Fig. 2** BOLD signal time courses of activated clusters by mechanical pain stimulation in the HS group. The mean BOLD signal time courses of activated clusters in the HS group. A *dotted box* indicates the duration of pain stimulation. *Error bars* indicate standard errors of the mean. *R* right, *L* left, *IC* insular cortex, *ACC* anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex

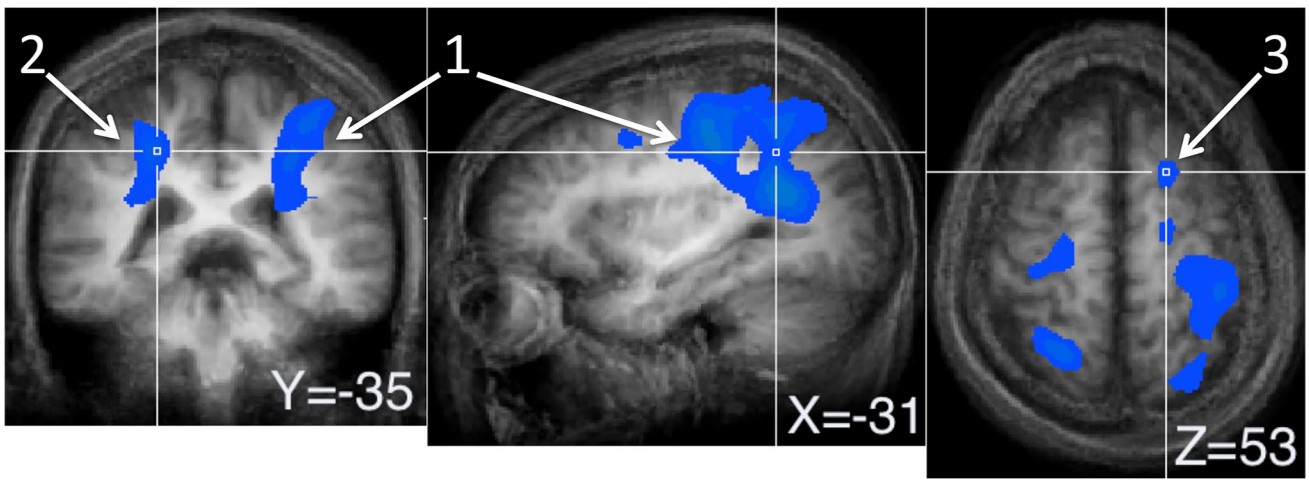


**Fig. 3** Cerebral deactivation by mechanical pain stimulation in the cLBP group. Cerebral deactivation was observed under mechanical pain stimulation at 500 kPa at the lower back. Most of those areas belong to the default mode network. *1* Left superior parietal cortex, *2* right superior parietal cortex, *3* left premotor area

## Discussion

The most remarkable finding in the present study was that the cLBP patients lacked activation at the ACC and DLPFC in response to low back pain stimulation at 500 kPa as revealed by the HS-cLBP contrast analysis. Single- and between-group analyses revealed the bilateral activation of the DLPFC in HS. The ACC activation might also probably have spanned the both hemispheres, because the *x*-coordinate of the ACC cluster was located almost on the midline. Such bilateral distribution of pain-related areas accords with earlier neuroimaging studies on experimental pain [9, 13, 14].

Those areas have commonly been reported as part of the experimental pain-related areas in earlier studies [15], as well as in our previous report [6]. The ACC and DLPFC are

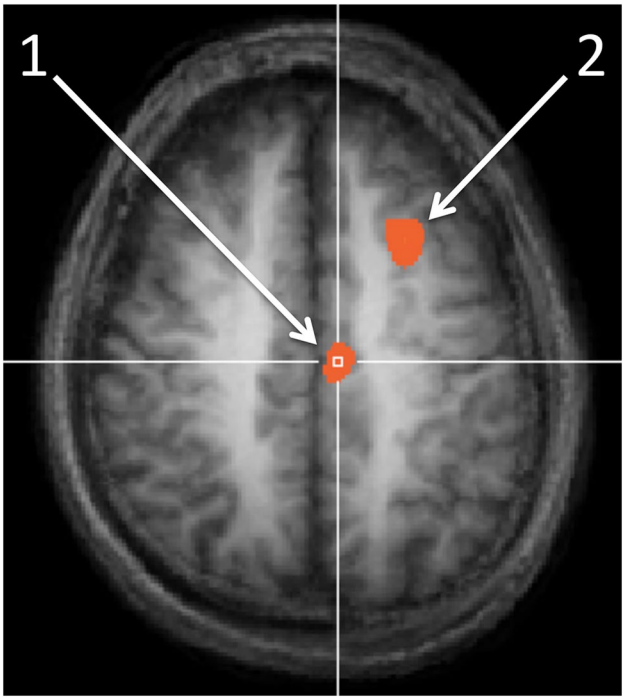


**Fig. 4** HS-cLBP contrast map during mechanical pain stimulation at the lower back. A between-group comparisons of multi-subject general linear model analysis revealed two significant clusters that showed higher activation in the HS group than in the cLBP group. *1* Left anterior cingulate cortex (BA32), *2* left dorsolateral prefrontal cortex (BA8)

considered to be areas that mediate affective and cognitive components of pain perception [16]. Recent human neuroimaging studies also suggested that those areas are the cortical origin of the descending pain inhibitory system [17, 18]. Pain-related activation of the ACC and DLPFC might potentially trigger a top-down process associated with the descending pain inhibitory system as implied by an earlier observation of placebo effect-related activation [19].

Therefore, the present findings might imply a possible inactivity of the ACC and DLPFC in the cLBP patients, which could have contributed to their intractable, persistent pain symptoms. This notion is supported by a significant correlation between the BOLD contrasts of the ACC and DLPFC and the overall severity of daily pain symptoms semi-quantified by the MPQ (Fig. 7). The absence of insular activation in the cLBP group might also be relevant to the decreased descending activity [18].

We also observed a significant deactivation in large areas of the superior parietal cortex in both the HS and cLBP groups. Those areas are part of the default mode network (DMN), which shows deactivation or a local blood flow decrease consistently over many sensory or cognitive tasks [8, 20]. We did not find any statistically significant differences between the groups in the BOLD amplitudes of the DMN, except for a slightly smaller negative BOLD amplitude at the right DMN in the cLBP group. A relative inactivity of the DMN was previously reported in cLBP patients, which was considered a possible basis for cognitive dysfunction in those patients [17]. A further functional connectivity analysis for the DMN might potentially reveal some differences in the activities of DMN in cLBP patients. Analysis of functional relationships between the descending pain modulatory system and the DMN might as well be a significant focus of further study [21].

We did not find any activation in the primary or secondary somatosensory cortices by the present method of pain stimulation, which was in accordance with our previous study [6]. A mechanical pressure stimulus at the lower back

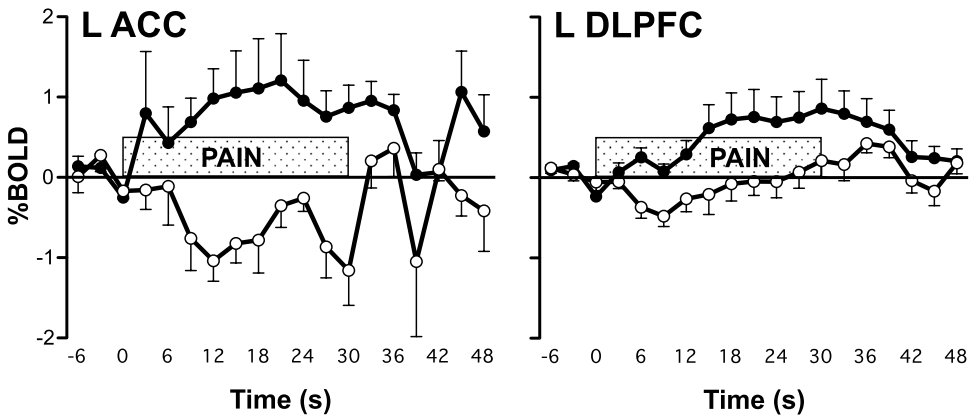


**Fig. 5** Contrasting BOLD signal time courses of the left ACC and the left DLPFC during mechanical pain stimulation in the HS and cLBP groups. In both areas, the BOLD signals were increased in the HS group but decreased in the cLBP group. A *dotted box* indicates the duration of pain stimulation. *Filled circles* HS group, *open circles* cLBP group. *Error bars* indicate standard errors of the mean. *L* left, *ACC* anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex

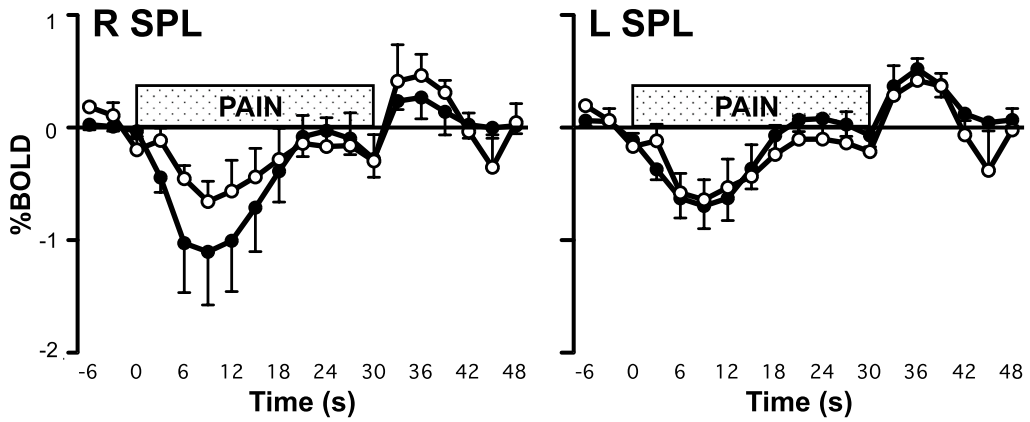


**Fig. 6** BOLD signal time courses of deactivation at the bilateral SPL during mechanical pain stimulation. The bilateral superior parietal cortices (SPL) showed similar time courses of deactivation during mechanical pain stimulation in both the HS and cLBP groups. Although not statistically significant, the maximal amplitude of deactivation at the right SPL was larger in the HS group than that in the cLBP group ($p = 0.059$). A *dotted box* indicates the duration of pain stimulation. *Filled circles* HS group, *open circles* cLBP group. *Error bars* indicate standard errors of the mean. *R* right, *L* left

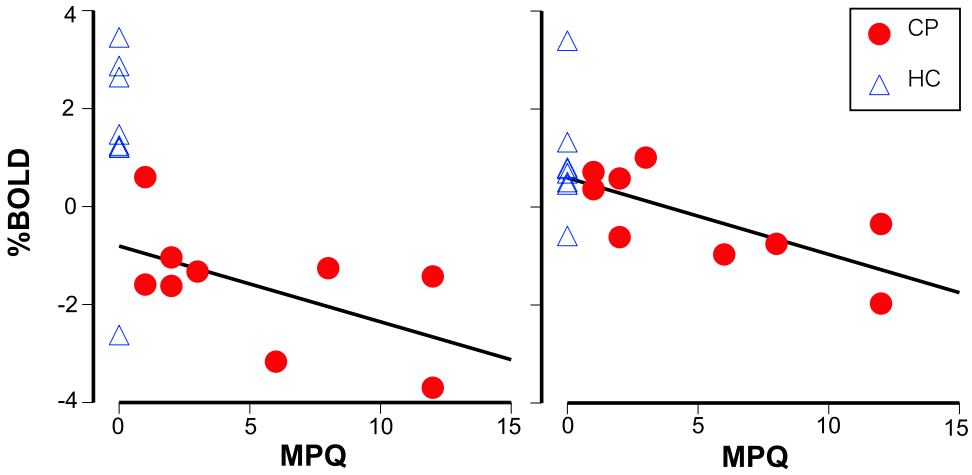


**Fig. 7** Correlations between the MPQ score and %BOLD signal changes. Activations at both the ACC and DLPFC were negatively correlated with the MPQ scores. *MPQ* scores of the McGill Pain Questionnaire Short Form, *CP* chronic pain patients, *HC* healthy control subjects, *L* left, *ACC* anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex

may not have elicited somatotopically oriented pain sensation, but deep tissue pain in the paraspinous musculature. Activation at the posterior cingulate cortex, insula, and prefrontal cortex was not reproduced in the cLBP patients, either, possibly due to a stricter statistical threshold than the previous study [6].

The present study has several limitations. First, the periaqueductal gray (PAG) was not within the field of view because of a significant susceptibility artifact below the anterior commissure-posterior commissure line. In future studies we will need to further examine the relationships between the cortical activities, at the ACC and DLPFC, and that of the PAG to determine whether those areas are functionally correlated in mediating the descending pain inhibitory system. Second, we had to use a relatively small sample size of subjects after removal of fMRI data sets with high motion or scanner artifacts. However, a robust contrast between the HC and cLBP, at $p < 0.05$ with multiple comparisons, might support probable reproducibility even with larger sample sizes. A marginal, but non-significant, difference in age between the groups (48 vs. 34 years in average) should not have affected the present findings of contrasting cortical activities, because age-related differences in experimental pain-related activation had been found exclusively in the basal ganglia between old and young adult subjects with a much larger age difference (79 vs. 26 years in average, respectively) [22, 23]. We did not find any between-group differences in activations at the basal ganglia in the current study. Third, to enhance the signal-to-noise ratio in fMRI data analysis, we performed signal thresholding at a BOLD signal intensity of 1000 (arbitrary value), removing susceptibility-related, unreliable BOLD signals especially at areas below the anterior commissure-posterior commissure line [24]. Such preprocessing helped in removing false-positive activations, but might potentially have concealed weak but true BOLD

signal changes associated with the present low back pain stimulation paradigm, especially around the orbitofrontal cortex and the basal ganglia.

In conclusion, we found that the cLBP patients in this study lacked activation at the ACC and DLPFC in response to mechanical pressure stimulus at 500 kPa on the lower back. This might imply a possible inactivity of the descending pain inhibitory system in those patients, which may at least partly explain the mechanisms of pain chronification in cLBP patients.

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**Compliance with ethical standards**

**Conflicts of interest** No authors declare any conflicts of interest.

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