

Original Article

Abnormal baseline brain activity in patients with cancer-induced bone pain: a resting-state functional magnetic resonance imaging study

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Abstract: *Objective:* To investigate the alternations of brain activities in patients with cancer-induced bone pain at resting state. *Methods:* The present study uses resting-state functional magnetic resonance imaging (fMRI) to explore functional brain activities in 12 lung cancer patients with cancer-induced bone pain, 12 lung cancer patients without cancer-induced bone pain, and 12 healthy controls. All of the lung cancer patients were in stage M1 at beginning of the study. The amplitude of low-frequency fluctuations (ALFF) was analyzed on the whole brain in all subjects. *Results:* There was significantly ALFF in the anterior cingulate cortex (ACC) and the medial prefrontal cortex (mPFC) in patients with cancer-induced bone pain in comparison with patients without cancer-induced bone pain. In addition, when compared with healthy controls, the patients with cancer-induced bone pain and patients without cancer-induced bone pain both showed altered activities, mainly in the posterior cingulate cortex (PCC). There was a significantly positive correlation between the visual analogue scale (VAS) and ALFF in the mPFC in patients with cancer-induced bone pain. *Conclusion:* Patients with cancer-induced bone pain displayed abnormal variations in baseline brain activity in some brain regions related to prefrontal-limbic network based on ALFF. All abnormalities in the brain regions may be viewed as a key marker and meanwhile could add insight into the judgment of the therapeutic effect of pain in patients with cancer-induced bone pain in future.

Keywords: Resting-state, amplitude of low-frequency fluctuations, cancer-induced bone pain, functional magnetic resonance imaging

Introduction

For people with bone metastasis, the ongoing pain is the most common symptom and can be excruciating. 30-40% of patients present the symptom of pain during early stages of the disease, and the number rises to 70-90% in advanced stages of the disease [1]. Patients with pain resulting from bone metastasis are highly maladaptive. Some studies have reported that severe pain of patients can result in anxiety and/or depression, which ultimately alters physiological processes [2-4]. The underlying brain mechanisms of pain in patients with cancer-induced bone pain are largely unknown. A neuroimaging approach will be utilized to gain a further understanding on this subject.

During the last few decades, the pathophysiological mechanisms of pain have been investigated with structural and functional neuroimaging

studies [5-9]. Human brain imaging studies indicate that different chronic pain syndromes exhibit distinct brain activities and that chronic pain is associated with functional/morphological alterations of brain [10-12]. Chronic pain seems to alter brain dynamics by changing interactions among brain intrinsic networks related to attention, reward, salience and default states at resting state [13]. The intrinsic activities of brain at rest appear to become unbalanced by chronic pain. Previous studies have demonstrated pain-induced disruption of spatial and temporal properties of the functional brain activity at resting state [11-15]. Nevertheless, very little is understood on the mechanisms and affected sites of the brain in patients with cancer-induced bone pain.

Resting-state functional magnetic resonance imaging is a non-invasive method of functional brain imaging. The resting brain activities are

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measured through changes in blood flow what is referred as blood-oxygen-level-dependent signal [16]. As already reported, relying on method of resting state analysis a number of brain networks have been discovered. These resting state networks consist of the human brain's intrinsic functional networks [16, 17]. Detecting abnormal brain activities may be considered a marker to reveal the progress state of diseases. The brain's intrinsic functional architecture has been widely visualized and measured through the resting-state fMRI in patients with several different medical disorders, for instance depression [18], Alzheimer [19], and Schizophrenia [20]. However, until now, rarely studies had identified the brain activities of resting-state networks in patients with cancer-induced bone pain.

In our study, we utilized ALFF to study the alterations of brain activities in patients with cancer-induced bone pain at resting state. These abnormalities may serve as a key marker and could add insight into the therapeutic effect of pain in patients with cancer-induced bone pain in future. We hypothesized that an abnormal ALFF is found at resting state in certain brain areas in patients with cancer-induced bone pain in comparison to patients without cancer-induced bone pain.

Materials and methods

Central South University (CSU) Institutional Review Board committee approved all the human fMRI experiment in the study. All participants gave informed consent according to guidelines set by MRI Center of Central South University.

Participants

A total of 36 participants, including 24 cancer patients and 12 healthy subjects, participated in this study. Cancer patients had been clinically diagnosed with stage M₁ lung cancer. The informed written consent was taken. Twelve right-handed patients with cancer-induced bone pain, twelve right-handed patients without cancer-induced bone pain, and twelve right-handed healthy subjects (control) from the Third Xiangya Hospital participated in this study. Exclusion criteria included tumor metastasis into the brain, other chronic pain conditions, history of head injury, head trauma, epilepsy and clinical depression, which excluded potential participants via the use of the Beck's Depression Inventory. Patients taking analge-

sics agents were instructed to stop taking these at least 7 days before the start of experiment. Before the functional scan, rate the spontaneous fluctuations of bone metastasis pain, by evaluating spontaneous fluctuations in the intensity of cancer patients' ongoing pain with a visual analogue scale (VAS) that ranged from 0 to 10, with zero representing no pain and 10 representing maximum pain. Subjects selected words that most closely described painful stimuli using Short McGill Pain Questionnaires.

Imaging protocol

A 1.5-T (Siemens; Tokyo, Japan) MRI scanner at the Third Xiangya Hospital in Hunan, China, was used to obtain images, and an Echo planar imaging (EPI) sequence was used to collect functional images. For every participant, 210 images were obtained using following imaging parameters: echo time = 40 ms; repetition time = 2000 ms; slice = 26; slice gap = 1 mm; Flip Angle = 90°; voxel size = 4 × 4 × 5 mm³; matrix size = 64 × 64. A high-resolution, three-dimensional T1-weighted structural image was also scanned with following parameters: Flip Angle = 15°; echo time = 2.92 ms; repetition time = 1900 ms; voxel size = 1 × 1 × 1 mm³; slice = 176; matrix size = 240 × 240. During 30 minute scanning, all participants were asked to keep their eyes closed, remain awake, and rest without thinking about anything in particular.

Data processing and analysis

SPM8 (<http://www.fil.ion.ucl.ac.uk/14k>), Statistical Parametric Mapping was used for carrying out imaging preprocessing. We discarded the beginning 10 volumes to eliminate any non-equilibrium effects of magnetization. Then, the resting 200 time points were corrected for acquisition delay between slices and realigned to the first image for head motion correction. No participants were excluded due to head motions exceeding 2 mm or 2° of rotation in any direction during fMRI scanning [21]. The functional images were spatially normalized to the standard SPM8 Montreal Neurological Institute (MNI) template, re-sampled to 3 mm cubic voxels, and smoothed by a Gaussian kernel with the full width set at a half maximum of 8 mm.

ALFF calculation

REST software (<http://resting-fmri.sourceforge.net>) was used for ALFF analysis and further data pre-processing in SPM8 after pre-pro-

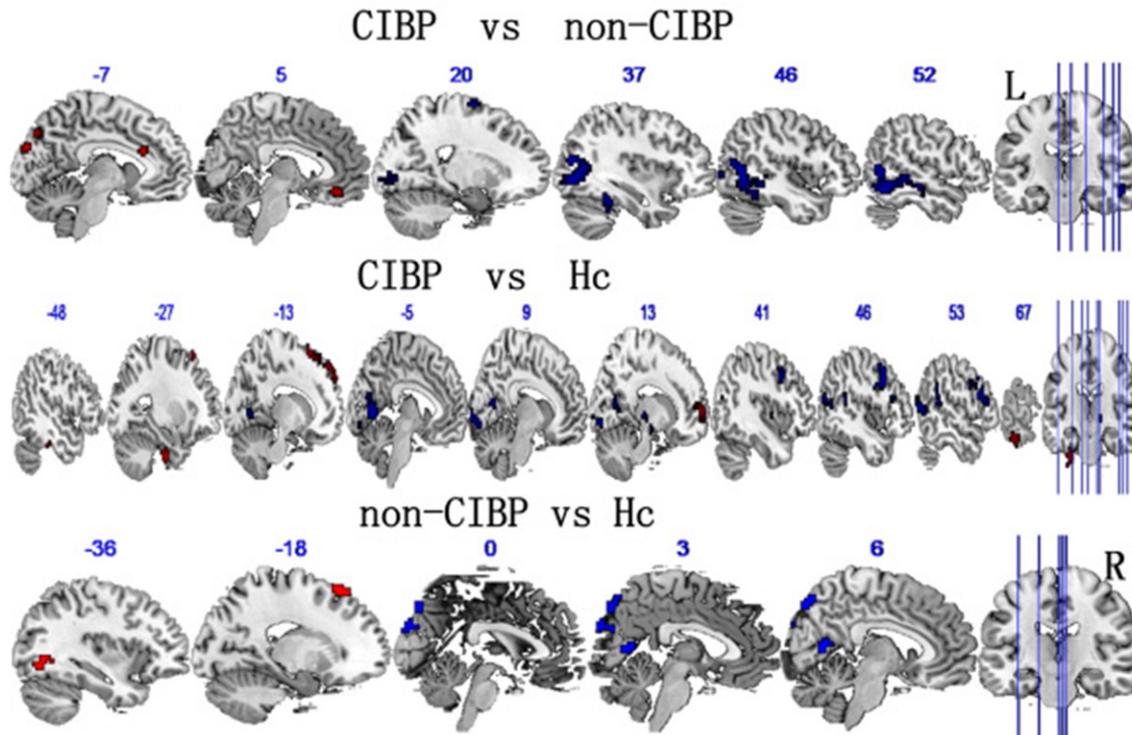


Figure 1. Significant differences in ALFF among patients with cancer-induced bone pain (CIBP), patients without cancer-induced bone pain (non-CIBP), and healthy controls (Hc). The Statistical parametric map exhibiting red areas indicate increased ALFF, and blue areas indicate decreased ALFF. The numbers over the images refer to the z-coordinates of the Montreal Neurological Institute (MNI) template. The threshold for display was set to $P < 0.05$ (FDR corrected), cluster size $\geq 432 \text{ mm}^3$.

cessing. Primarily, the linear trend must be removed and every voxel was band-pass filtered (0.01~0.08 Hz) to remove the effects of low-frequency drift and high-frequency noise. The interference of head motion was then eliminated using linear regression, but white matter and cerebral cerebrospinal fluid (CSF) were not regressed out. The procedure for the ALFF calculation is as follows: 1) The filtered time series was transformed to a frequency domain with a fast Fourier transform; 2) After obtaining power spectrum, square root was calculated at each frequency of the power spectrum and then across 0.01 Hz to 0.08 Hz each voxel the averaged square root was averaged to calculate the ALFF; 3) For standardization purposes, the mean was subtracted and divided by global standard deviation to convert the resulting ALFF into z-scores [22].

Statistical analysis

For the comparison among groups, a two-sample t-test was performed to examine ALFF dif-

ferences amongst: (1) cancer patients with bone metastasis pain, (2) cancer patients without bone metastasis pain patients, (3) healthy volunteers. Significant clusters (cluster size $\geq 432 \text{ mm}^3$, 16 voxels) of activation for the two sample t-tests were determined by using a ($P < 0.05$) FDR corrected threshold. Using the Monte Carlo simulations, we determined this correction on REST software.

Correlation analysis

An analysis of partial correlation between ALFF values and visual analogue scale (VAS) outcomes was performed to give a test in correlation of ALFF abnormality and intensity of pain in patients with bone metastasis pain. It showed the most significant differences between the bone metastasis pain group and the non-bone metastasis pain group. Anatomical Automatic Labeling atlas toolbox [23] defined the intersection of the corresponding region, which means each of the clusters and the within group two sample t-test map allowing for threshold set at $P = 0.05$.

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Table 1. Showing altered ALFF of brain regions between CIBP and non-CIBP

Brain regions [BA: Brodmann Area]	Volume (Number of voxels)	P	T	PX	PY	PZ
<i>CIBP < non-CIBP</i>						
Right middle temporal gyrus/right middle occipital gyrus	400	0.04	-6.1739	42	-63	12
Right lingual gyrus [17]	23	0.01	-3.5875	18	-87	0
Right superior frontal gyrus [6]	17	0.01	-4.8251	24	-3	69
<i>CIBP > non-CIBP</i>						
Right medial frontal gyrus	15	0.01	4.0087	3	42	-18
Anterior cingulate gyrus [24]	16	0.02	4.9619	-6	24	21
Left cuneus [19]	20	0.03	4.0773	-6	-90	27
Left precuneus	17	0.01	3.961	-9	-81	42

Table 2. Showing altered ALFF of brain regions between CIBP and Hc

Brain regions [BA: Brodmann Area]	Volume (Number of voxels)	P	T	PX	PY	PZ
<i>CIBP < Hc</i>						
Right lingual gyrus [17]	61	0.03	-5.0611	0	-84	-9
Left posterior cingulate gyrus	110	0.04	-5.2584	-6	-66	3
Right middle temporal gyrus	52	0.01	-4.191	57	-72	9
Right superior temporal gyrus	33	0.04	-4.2201	54	-42	12
Right inferior frontal gyrus	38	0.04	-5.096	51	27	15
<i>CIBP > Hc</i>						
Left temporal lobe [20]	44	0.02	6.7886	-66	-24	-27
Right temporal lobe [20]	32	0.01	3.721	66	-33	-18
Left superior frontal gyrus	101	0.05	4.6776	-21	30	60
Right medial frontal gyrus	37	0.04	4.0403	12	60	9
Left fusiform gyrus [20]	31	0.01	4.5221	-36	-21	-4

Results

Generic parameters

Based on clinical and demographic characteristics of all subjects, gender and age ($t = 1.297$, $P = 0.186$; $t = 1.712$, $P = 0.240$) had not significant differences among three groups. For VAS ($t = 9.268$, $P < 0.001$), scores of patients with cancer-induced bone pain were significantly higher than those of cancer patients without cancer-induced bone pain.

Brain activity for spontaneous pain

Patients with cancer-induced bone pain (CIBP) versus patients without cancer-induced bone pain (non-CIBP): Compared with CIBP, non-CIBP showed a decreased ALFF in right middle occipital gyrus, the right middle temporal gyrus, right superior frontal gyrus and right lingual gyrus. The opposite relationship was observed in the

right medial frontal gyrus, left cuneus, anterior cingulate gyrus and precuneus. In **Figure 1** and **Table 1**, specific contents including clusters and Montreal Neurological Institute (MNI) coordinates are shown.

Patients with cancer-induced bone pain (CIBP) versus healthy controls (Hc): In **Figure 1** and **Table 2**, the group differences between CIBP and Hc are shown. The ALFF in CIBP was higher than in Hc in the left superior frontal gyrus, temporal lobe, right medial frontal gyrus and fusiform gyrus. The ALFF was found to

be significantly lower in CIBP than in Hc in inferior frontal gyrus, right middle temporal gyrus, the left posterior cingulate gyrus, right lingual gyrus and right superior temporal gyrus.

Patients without cancer-induced bone pain (non-CIBP) versus healthy controls (Hc): As shown in **Figure 1** and **Table 3**, the group of (Hc) demonstrated a decreased ALFF in the right precuneus, the left cuneus and right posterior cingulate gyrus in comparison with healthy volunteers. Conversely, left occipital lobe and the left superior frontal gyrus demonstrated an increased ALFF in non-CIBP.

Statistical correlations between VAS and ALFF values

The statistical correlations between VAS and ALFF values in brain regions, including mPFC and ACC, with significant group differences

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Table 3. Showing altered ALFF of brain regions between non-CIBP pain and Hc

Brain regions [BA: Brodmann Area]	Volume (Number of voxels)	P	T	PX	PY	PZ
<i>Non-CIBP < Hc</i>						
Right posterior cingulate gyrus	19	0.02	-4.7369	6	-63	12
Right precuneus	32	0.01	-6.4373	3	-78	48
Left cuneus	26	0.01	-4.8602	0	-87	30
<i>Non-CIBP > Hc</i>						
Left superior frontal gyrus	26	0.02	5.1674	-18	21	60
Left occipital lobe	15	0.03	4.7132	-36	-72	-6

(CIBP verse. non-CIBP) were examined. A significant statistical correlation was found only between VAS and ALFF values in mPFC ($r = 0.771$, $P = 0.003$).

Discussion

The goal of this study was to investigate the alterations in resting-state brain activities in patients with bone metastasis pain using fMRI, and we found an increased ALFF the right medial frontal gyrus, left cuneus, anterior cingulate gyrus and precuneus in patients with cancer-induced bone pain when compared with patients without cancer-induced bone pain. Inversely, a decreased ALFF (CIBP < non-CIBP) was observed in right middle occipital gyrus, the right middle temporal gyrus, right superior frontal gyrus and right lingual gyrus. When compared with healthy controls, the patients with cancer-induced bone pain and patients without cancer-induced bone pain both displayed changed activities, mainly in the posterior cingulate gyrus. In addition to this, there was a significant positive correlation between the VAS and ALFF in the mPFC in patients with cancer-induced bone pain.

The frontal cortex is one of the most prominent areas associated with abnormal brain activities in chronic pain. Multiple factors can contribute to sustained mPFC activity after decrement of the nociceptive elicitor [24]. Previous studies have suggested that the mPFC may play a specific role in mediating the attenuation of pain perception via cognitive control mechanisms and that the mPFC is involved in response conflict, detection of unfavorable outcomes and emotions [24, 25]. Therefore, cognitive and mental disorders may arise from abnormal

activity in the mPFC. This abnormal activity may partly contribute to cognitive decline and a lack of interest or pleasure in patients with chronic pain. Using resting-state fMRI, the current research perceived an increased ALFF in the mPFC in patients with cancer-induced bone pain in contrast to patients without cancer-induced bone pain.

There was also a positive correlation between VAS and ALFF values within mPFC. In line with our results, hyperactivity of mPFC in association with pain has been determined by previous studies [26-29], which may be considered as a critical trait marker for chronic pain. Prior study has already demonstrated an increase in the firing activities of mPFC neurons during the delay period in delayed-choice task [30], which suggests that working memory processing may rely heavily on increased activity of mPFC in the experiment. This is in accordance with suggestion that mPFC instability may play a crucial role in pain-induced memory dysfunction. Cross-sectional fMRI studies indicate that mPFC, encoding fluctuations of ongoing pain in multitudinous chronic pain syndromes, is prior to take part in the brain's emotion and limbic circuitry [31]. Particularly, in chronic back pain, spontaneous pain primarily activates the mPFC [24]. Frank Seifert et al. [32] found that during hyperalgesia, activity increase was found in mPFC and posterior cingulate gyrus (PCC). Activity in mPFC correlates inversely with the individual's extent of central hyperalgesia and predicts the individual's pharmacological antihyperalgesic treatment response. With the help of these results, it can be speculated that hyperactivity in mPFC may be a principal element of the development and progression of cancer-induced bone pain.

Pain perception is also modulated through important cerebral influences on the limbic system. ACC is an important limbic system area for pain-related perception. In this study, we have shown that activity is increased within the ACC in patients with cancer-induced bone pain. Previous research has demonstrated that the ACC results of acute pain in healthy partici-

pants versus participants with chronic pain are significantly different [33]. Involvement of the ACC, one of the most commonly studied regions regarding acute pain and chronic pain, is highly prominent in pathological pain. Acute nociceptive responses in patients with lesions of the ACC were significantly increased [34], and studies based on human beings manifest that ACC activity is involved in social exclusion due to pain, the empathy of pain, chronic migraine and hypothesized pain [35, 36]. A meta-analysis on the structure and function of the ACC indicated that ACC activations found in neuroimaging studies of pain predominantly reflect affective pain processing [37]. The suppression of affective responses to a negative stimulus was associated with the activity of the ACC. It is true that the ACC, which plays a crucial role in emotion generation and regulation, is connected with the mPFC, the amygdale, and the hippocampus. Thus, the increased activity in ACC in patients with cancer-induced bone pain may give rise to an imbalance of mPFC-activated influence on activities leading to affective pain. Our data, however, cannot declare that the observed increase of activity levels in the ACC is due to the variational relevance between ACC and mPFC. On the basis of previous studies, we believe that this conceive should be examined in the following studies.

The active brain regions, including the mPFC and the ACC, found to have an increased ALFF in patients with cancer-induced bone pain are both a part of prefrontal-limbic network that plays an important role in affective pain processing. It is likely that interactions between intrinsic resting state networks and networks of brain areas that receive nociceptive input become dysfunctional in pain states. Existence of patients with pain exhibiting abnormal variations in brain regions of prefrontal-limbic network has been demonstrated in previous brain imaging studies. In this study, we found the existence of patients with cancer-induced bone pain having aberrant neural activities in prefrontal-limbic network, bringing about a potential insight to the neurobiological mechanisms of pain in patients with cancer-induced bone pain.

In opposition to the increased activities in brain regions located at prefrontal-limbic network, this study detected a decreased ALFF in the

posterior cingulate cortex (PCC) when compared with Hc in both patients with cancer-induced bone pain and patients without cancer-induced bone pain. In a meta-analysis, Nielsen FA et al. showed that instances of memory activation are predominantly found in the caudal part of the PCC, whereas pain is found in the rostral part of the PCC [38]. In a previous study, PCC was linked to stimuli intended to elicit a feeling of disgust rather than a feeling of pain [39]. Significant PCC activation was detected during the painful stimulations of patients with chronic pain. In recent studies, Han S. Duke et al. used resting-state fMRI approaches and found that patients with chronic musculoskeletal pain were provided with different pattern of functional brain activities. Notably, these patients displayed greater functional connectivity of PCC to the left superior temporal gyrus, left cerebellum and left insula [40]. In addition, J Keltner et al. found that HIV-associated neuropathic pain is associated with smaller ventral PCC [41]. In our study, during spontaneous painful stimulations to patients with cancer-induced bone pain, activation of PCC seems to be the main distinguishing difference. However, cancer-induced bone pain is a complicated disorder implicated by the triad of anxiety, depression, and pain. Whether this change of PCC of pain processing is causative to the cancer-induced bone pain state or merely follows the adverse experience of the patients cannot be deduced from our data.

In summary, this study used ALFF to investigate differences between patients with cancer-induced bone pain and patients without cancer-induced bone pain in the resting state. We discerned that there are abnormal activities in some brain regions related to prefrontal-limbic network in patients with cancer-induced bone pain. Our study not only broadens the knowledge regarding pain in patients with cancer-induced bone pain, but it also brings in a potential vision about the ultimate neurobiological mechanisms behind high incidence of cancer-induced bone pain in patient. Our results support that among patients who experience chronic cancer-induced bone pain, a network of regions exists at rest that is continuously ready to process the physiological modulators of pain. To our knowledge, this is the first resting-state fMRI study on cancer-induced bone pain in patients with bone metastasis.

Conclusion

In this study, we confirm and extend the findings that the baseline of neuronal activity of spontaneous pain changes in patients with cancer-induced bone pain. The impact of sustained spontaneous cancer-induced bone pain may lead to abnormal changes in baseline brain activity in some brain regions related to prefrontal-limbic network based on ALFF, which subsequently highlights the ultimate neurobiological mechanisms behind clinical cancer-induced bone pain symptoms.

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Disclosure of conflict of interest

None.

Abbreviations

ALFF, amplitude of low-frequency fluctuations; Mpf, medial prefrontal cortex; VAS, visual analogue scale; ACC, anterior cingulate cortex; fMRI, functional magnetic resonance imaging; PCC, posterior cingulate cortex.

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