Surface-based Map Plasticity of the Sensorimotor Cortex in Hip Disorder at Local and Extensive Levels: A Resting-state fMRI Study

Jie Ma
School of Rehabilitation Science

Xu-Yun Hua
Department of Traumatology and Orthopedics

Mou-Xiong Zheng
Department of Traumatology and Orthopedics

Jia-Jia Wu
Center of Rehabilitation Medicine

Bei-Bei Huo
School of Rehabilitation Science

Xiang-Xin Xing
School of Rehabilitation Science

Sheng-Yi Feng
Department of Traumatology and Orthopedics

Bo Li
School of Rehabilitation Science

Jian-Guang Xu (✉️ xjg@shutcm.edu.cn)
School of Rehabilitation Science Shanghai University of Traditional Chinese Medicine, Shanghai, China

Research

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Abstract

**Background:** Pain is one of the manifestations of hip disorder and has been proven to lead to the remodeling of somatotopic map plasticity in the cortex. However, it’s not clear whether hip disorder with pain induces somatotopic map plasticity in the cortex. We aimed to evaluate the surface-based map plasticity of the somatotopic cortex in hip disorder at local and extensive levels by resting-state functional magnetic resonance imaging (rs-fMRI).

**Methods:** 20 patients with osteonecrosis of the femoral head (ONFH) (12 males and 8 females, age=56.80±13.60 years) with Visual Analogue Scale (VAS) scores ≥ 4 and 20 healthy controls (9 males and 11 females, age= 54.56±10.23 years) were enrolled in this study. rs-fMRI data and T1 imaging data were collected, and surface-based regional homogeneity (ReHo), seed-based functional connectivity (FC), cortical thickness and the volume of subcortical gray nuclei were calculated.

**Results:** Compared with the healthy controls, the ONFH patients showed significantly increased surface-based ReHo in areas distributed mainly in the left dorsolateral prefrontal cortex and frontal eye field, the right frontal eye field and the premotor cortex and decreased surface-based ReHo in the right primary motor cortex and primary sensory cortex. When the area with decreased surface-based ReHo in the frontal eye field and right premotor cortex was used as the regions of interest (ROI), compared with the controls, the ONFH patients displayed increased FC in the right middle frontal cortex and right inferior parietal cortex and decreased FC in the right precentral cortex and right middle occipital cortex. ONFH patients also showed significantly decreased cortical thickness in the para-insular area, supplementary motor cortex area and frontal eye field and decreased volume of subcortical gray matter nuclei in the right nucleus accumbens (479.32±88.26 vs 539.44±68.36, P=0.026).

**Conclusions:** Hip disorder patients showed cortical plasticity changes, mainly in sensorimotor and pain-related regions.

**Background**

Osteonecrosis of the femoral head (ONFH), also known as avascular or ischemic necrosis of femoral head, is a hip disorder and challenging orthopedic disease that severely diminishes patient quality of life. The risk factors of ONFH are varied and include physical trauma, smoking, excessive alcohol consumption, autoimmune diseases, coagulation disorders, hemoglobinopathies, corticosteroid therapy and other factors. ONFH is a progressive pathological process characterized by ischemia, necrosis, and eventually collapse. Despite no predominant pattern of a clinical presentation, pain and dysfunction of the joint seem occur frequently in ONFH. Pain presents in only half of patients with no limitation of activity in the early stages but almost always appears in later stages. The disease generally progresses to collapse and eventually painful osteoarthritis if symptomatic ONFH has not been treated. The treatment strategy of ONFH depends on the disease stage. Reducing pain is one of the main goals of early treatment. Total hip arthroplasty (THA) in patients with osteonecrosis is widely used to improve
patient quality of life. However, revision surgeries after THA in young patients are common, and thigh pain is a common complaint after THA\(^5\). This pain is a primary factor influencing patients’ dissatisfaction after THA\(^6\).

As observed in ONFH, joint diseases cause pain, and the impaired joints and surrounding muscles, ligaments and tendons can cause proprioception abnormalities. Such abnormal sensory perception leads to the remodeling of the sensory cortex. The mature human primary somatosensory cortex can reorganize itself in response to changes in sensory input, displaying strong plasticity capacity. Following the elimination of afferent return, there is a well-known ‘invasion’ of the deafferented region of the brain by the cortical representation zones of still-intact portions of the brain adjacent to it\(^7\). Human and animal studies have confirmed that sensory deprivation can induce somatotopic map plasticity in the primary somatosensory cortex\(^7,8\). Prolonged and chronic pain can both alter neural plasticity at the cortical level\(^9\).

It has gradually been recognized that cerebral processes contribute to pain beyond the level of nociceptive input and contact behavioral and psychological influences\(^10\). Pain is a complex sensory and emotional experience that is shaped by psychobiology, expectations from past and learned pain experiences and attention processes\(^11\). In a study of intestinal diseases related to abdominal pain, researchers found altered neural modulation of pain in affective and cognitive brain regions, including the cingulate cortex\(^12\). Brain regions of headache patients showed significant activations in areas responsible for the processing of cognitive empathy\(^13\). Current theories describe the brain activity of pain as abnormal functioning in large-scale networks that include non-nociceptive regions\(^14,15\). Chronic cervical spondylotic pain, chronic back pain and knee osteoarthritis show functional anomaly during the pain process\(^16,17\). Subjects with cruciate ligament deficiency also exhibit increased activation in the secondary somatosensory area (where pain and sensory processing occur)\(^18\).

The remodeling of somatosensory cortex evidences the plasticity of the somatotopic map \(^19\). Recently, somatosensory cortex stimulation has been proposed as a possible treatment for deafferentation pain after amputation\(^20\). Exploring the map plasticity in patients with ONFH can provide insight into its possible treatment. Therefore, based on previous studies that have discovered abnormal brain activity in many kinds of diseases related to sensory abnormality, we hypothesized that ONFH with pain may induce somatotopic map plasticity in cortex and yield a characteristic pattern of brain neural activity. Volume-based normalization may introduce inaccuracies in anatomical positioning of functional data\(^21,22\), and it is difficult to account for inter-subject variability in gyrus size, shape or position in a 3D referential; furthermore, such differences may correspond to the displacement of a functional focus to a different gyrus in some subjects\(^22\). As a large part of the data originates from the cortex, methods that work on the cortical surface may be more sensitive than those using the full brain volume and thus be more suitable for map plasticity study.

Diverse approaches can be used to detect map plasticity, including genetics analysis, synaptic and in vivo physiology analysis, optical imaging, and ultrastructural analysis\(^19\). Although these methods show excellent validity and reliability, they are not simple or convenient to use in the human body. An article
published in the New England Journal of Medicine reported increased activity in the stable patterns across regions that are associated with experimentally induced acute pain and tonic pain in healthy people. They proposed that a functional magnetic resonance imaging (fMRI) could be used to assess pain\(^{23}\). Resting-state functional magnetic resonance imaging rs-fMRI (rs-fMRI), as a convenient and noninvasive method, has been widely used in the evaluation of central remodeling in various diseases related to pain. Therefore, in our study, we chose fMRI as the assessment tool to test our hypothesis. To comprehensively understand the characteristics of somatotopic map plasticity in patients with ONFH, an understanding of the roles of pain-related brain regions and functional connections is needed. Therefore, among several functional measures of fMRI, surface-based regional homogeneity (ReHo)\(^{24}\) and seed-based functional connectivity (FC)\(^{25}\) were chosen to analyze localized and remote changes in brain functions. Compared with 3D ReHo, surface-based ReHo has higher test-retest reliability and can more clearly reveal the intrinsic functional organization of cortex\(^{26}\), which could be extremely useful for integrating various measures of both the structure and function of the cortical surface\(^{27}\). Cortical thickness and the volume of subcortical gray nuclei were also analyzed in the study.

**Materials And Methods**

**Clinical Samples**

A total of 20 right-handed ONFH inpatients without surgery (12 males and 8 females, age= 56.80±13.60 years) who were consecutively recruited and 20 right-handed healthy controls (9 males and 11 females, age= 54.56±10.23 years) were enrolled in this study. Diagnosis of ONFH was made based on magnetic resonance imaging (MRI) and clinical demonstrations. Patients were included if they had joint pains in groin, buttock and thigh areas and Visual Analogue Scale (VAS) scores for pain\(^{28}\) ≥ 4 over 1 year. Individuals were excluded from the study if they had a history of cardiovascular or cerebrovascular disease, ankylosing spondylitis, rheumatoid arthritis, hip dysplasia, metabolic disorders, or bone tumor. Informed consent was obtained from all participants included in the study. There was no statistical difference in background data between ONFH patients and healthy controls, including education, past history and operation history.

**MRI Data Acquisition**

MRI data were acquired using a MAGNETOM Verio 3.0 T scanner (Siemens Healthcare, Germany).

1. Functional imaging

rs-fMRI data were obtained with eye closed and a single-pass gradient recalled EPI sequence with the following protocols: interleaved scanning order, slice number=43, flip angle=90°, matrix size=64×64, TR=3000 ms, slice thickness=3.0 mm, FOV=230×230 mm\(^2\), gap=0 (voxel size 3.6×3.6×3.0 mm\(^3\)), and number of acquisitions=200.

2. Structural imaging
T1-weighted magnetization-prepared rapid acquisition was performed with the following parameters: repetition time/inversion time/echo time = 1900/900/2.93 ms, flip angle = 9°, FOV = 256 × 256 mm$^2$, section thickness = 1.0 mm sagittal acquisition, acquisition matrix = 256 × 256, number of averages = 1.

Data processing

Functional and structural images of each subject were preprocessed by using DPABI$^{29}$ (DPARSurf V4.3), which is based on Statistical Parametric Mapping (SPM12) (http://www.fil.ion.ucl.ac.uk/spm), on a MATLAB 2013b platform. Preprocessing was performed as previously reported$^{30}$. (1) slice scan time correction; (2) head movement correction (the head movements were all less than 2.5 mm or 2.5 degrees in any direction); (3) spatial normalization; (4) regression of nuisance variables (the white matter and cerebral spinal fluid blood oxygen level dependent (BOLD) signal and the effects of head motion using six head motion profiles). Then, ReHo and FC were calculated for the traditional low frequency band (0.01–0.10 Hz). Spatial smoothing (FWHM = 6 mm) was performed after surface-based ReHo calculation as in previous studies$^{30}$. Regions showing significant differences in surface-based ReHo values between the two groups were defined as regions of interests (ROIs) for seed-based FC analysis to investigate interregional functional synchronization, and FC calculation was performed as in previous studies$^{31}$.

Statistical analysis

Two-sample t-tests were performed by using SPSS to evaluate differences in the volume of subcortical gray nuclei between ONFH patients and healthy controls. The level of two-tailed statistical significance was set at $P < 0.05$. Two-sample t-tests were used for analyses of surface-based ReHo and cortical thickness differences between the ONFH patients and healthy controls. The results were corrected for multiple comparisons, with a combined threshold of a single voxel ($P < 0.05$). A more strict threshold ($P < 0.01$, cluster size $> 50$ voxels) was also used for each cohort to reduce the possibility of false negative results. Two-sample t-tests were used to analyses FC differences between the ONFH patients and healthy controls. We employed a cluster-level family-wise error (FWE) correction for multiple comparisons ($P < 0.05$).

Sample size calculation

This is a cross-sectional study. The essence of fMRI image is digit, fMRI data is measurement data. We planned a study of a continuous variable from independent control subjects (healthy controls) and experimental subjects (ONFH). Considering a true difference in the experimental and control means of 0.07 in ReHo, we needed to study at least 18 experimental subjects and 18 control subjects to be able to reject the null hypothesis that the population means of the experimental and control were equal with probability (power) 0.80. The type I error probability associated with this test of this null hypothesis was 0.05 ($\alpha$).

Results
Comparison of functional images between ONFH patients and healthy controls

Compared to healthy controls, ONFH patients showed significantly increased surface-based ReHo in areas distributed mainly in the left dorsolateral prefrontal cortex and frontal eye field, the right frontal eye field and premotor cortex and decreased surface-based ReHo in the right primary motor cortex and primary sensory cortex (Figure 1 and Table 1).

Regions showing significant differences in surface-based ReHo values between the two groups were defined as ROIs for seed-based FC analysis. As shown in Figure 2, when the area with decreased surface-based ReHo in the right frontal eye field and premotor cortex was used as ROI, the ONFH patients displayed increased FC in the right middle frontal cortex and right inferior parietal cortex and decreased FC in the right precentral cortex and right middle occipital cortex (Figure 2 and Table 2). FC values of another two ROIs did not significantly differ between the two groups.

Comparison of structural images between ONFH patients and healthy controls

Compared to healthy controls, ONFH patients showed significantly decreased cortical thickness in areas mainly distributed in the para-insular area, posterior insular area, anterior superior temporal area, frontal eye field and supplementary motor cortex. In addition, comparison of the volume of subcortical gray matter nuclei between the two groups revealed significantly decreased values in the right nucleus accumbens in ONFH patients compared with healthy controls (479.32±88.26 vs 539.44±68.36, P=0.026; Figure 3 and Table 3).

Table 1: Comparison of surface-based ReHo values between ONFH patients and healthy controls

| Overlap of atlas region                                      | Hemisphere | Cluster size | Cluster centroid MNI Coordinates | Peak t-value |
|--------------------------------------------------------------|------------|--------------|----------------------------------|--------------|
| 42.86% dorsolateral prefrontal cortex(9-46d)                 | L          | 55.62        | 6.28                             | 79.50        | 28.10 | 3.66 |
| 28.57% frontal eye field(8Ad)                                |            |              |                                  |              |
| 28.57% dorsolateral prefrontal cortex(9p)                    |            |              |                                  |              |
| 88.89% frontal eye field(8Av)                                | R          | 67.25        | 6.28                             | 52.78        | 38.68 | 4.09 |
| 11.11% premotor cortex and frontal eye field(i6-8)           |            |              |                                  |              |
| 95% primary sensory cortex(3a,3b)                            | R          | 56.91        | -14.74                           | -12.42       | 70.83 | -4.01 |
| 5% primary motor cortex(4)                                   |            |              |                                  |              |
Table 2: Comparison of FC values between ONFH patients and healthy controls

| Region Label                          | Cluster size | Cluster centroid MNI Coordinates | t-value |
|--------------------------------------|--------------|----------------------------------|---------|
|                                       |              | X      | Y      | Z      |         |
| right middle frontal cortex           | 2233         | 42     | 23     | 53     | 9.12    |
| right inferior parietal cortex        | 829          | 50     | -55    | 52     | 7.23    |
| right precentral cortex               | 999          | 15     | -27    | 65     | -9.25   |
| right middle occipital cortex         | 202          | 42     | -74    | 3      | -6.90   |

Table 3: Comparison of cortical thickness between ONFH patients and healthy controls

| Overlap of atlas region                | Hemisphere | Cluster size | Cluster centroid MNI Coordinates | Peak t-value |
|----------------------------------------|------------|--------------|----------------------------------|--------------|
|                                        |            |              | X      | Y      | Z      |         |
| 64.89% para-Insular area (PI)          | R          | 79.73        | 20.43  | 27.12  | -38.44 | -3.48   |
| 24.04% posterior Insular area (PoI1)   |            |              |        |        |        |         |
| 11.07% anterior superior temporal area (TA2) |          |              |        |        |        |         |
| 70.65% supplementary motor cortex and frontal eye field | R          | 67.69        | -19.30 | 54.03  | 53.80  | -4.14   |
| 29.35% supplementary motor cortex |            |              |        |        |        |         |

Discussion

In this study, we revealed differences in functional and structural imaging between ONFH patients and healthy controls that may reveal the characteristics of altered central pain processing in ONFH patients. The brain regions exhibiting differences between the two groups included the dorsolateral prefrontal cortex, frontal eye field, premotor and supplementary motor cortex, primary motor cortex, primary sensory cortex, middle frontal cortex, inferior parietal cortex, precentral cortex, middle occipital cortex, insula and
nucleus accumbens. These regions are mainly sensorimotor and pain-related regions. Our functional and structural analyses both support previous neuroimaging findings regarding pain and provide novel findings that may provide the foundation for future larger studies in ONFH.

Pain is one symptom of ONFH and is usually confined to the groin area, occasionally involving the ipsilateral hip and knee or greater trochanteric area. There are two complementary pathways related to pain processing: the medial and lateral pain pathways. In the present study, ONFH patients showed functional decline in the primary sensory cortex, which is compatible with the existence of complementary pathway related to pain processing and align with the results of brain function studies in other non-central nervous system diseases with pain. Interestingly, both of these pathways involve the insular cortex. In the pain matrix, the insular cortex is mainly involved in discriminative sensory and motivative emotion. Abnormal signal transmission from the injury site causes neuropathic pain, which generates enhanced synaptic plasticity. Our study showed decreased cortical thickness of the insular cortex, which is consistent with the findings of other pain studies in chronic migraine, cervical spondylosis with neck pain and irritable bowel syndrome. Usui C et al. observed that patients with fibromyalgia showed a significant difference in connectivity between the insular cortex and other brain regions. After analgesic treatment, the insular cortex is activated in low back pain and fibromyalgia. We also observed that the volume of the nucleus accumbens was significantly decreased in the ONFH patients compared with the healthy controls. Makary MM et al. provided evidence that a lower nucleus accumbens volume confers risk for developing chronic pain and that altered nucleus accumbens activity is a signature of the state of chronic pain.

Numerous studies have demonstrated that pain processing can shift from nociceptive somatosensory pathways to emotional brain circuits. Increased activation of the prefrontal cortex (PFC) is related to decreased pain and inhibits the functional connectivity between the midbrain and the medial thalamus. Further projections from the anterior cingulate cortex to the PFC may also be involved in cognitive appraisal of the stimulus. In addition, prefrontal responses to pain depend on the psychological state of the subject, who may expect worse pain or a reduction in pain. Neuroimaging studies indicate that upregulation and downregulation of negative emotions are associated with increased activation of prefrontal regions. These observations demonstrate that the PFC plays an important role in pain processing. We found that ONFH patients showed significantly increased ReHo in the dorsolateral prefrontal cortex. Notably, the areas with significantly increased ReHo are in the central part of the PFC. The dorsolateral prefrontal cortex is functionally linked to the descending pain modulation system and has been implicated in top-down pain inhibition, including placebo analgesia. In another orthopedic disease, poor recovery of upper limb pain after surgical interventions for cervical spondylotic myelopathy was found to be associated with the dorsolateral prefrontal cortex. Similarly, during pain onset, a higher BOLD signal response in the dorsolateral prefrontal cortices was observed in fibromyalgia patients than in control subjects. Therefore, brain hyperactivation may be a mechanism underlying the generalized hypervigilance to salient stimuli in pain.
The sensorimotor cortex is another brain region closely related to the sensory cortex. The sensorimotor cortex includes somatosensory and motor regions and extends to the supplementary motor area (SMA) \(^{52}\). The FC analysis revealed differences in sensorimotor regions between ONFH patients and controls. These findings are consistent with a previous pain study that showed abnormal functional connectivity of sensorimotor cortex in primary dysmenorrhea patients \(^{53}\). Furthermore, some studies have confirmed a relationship between pain persistence and aberrant sensorimotor cortex activity \(^{54}\). Interestingly, in the present study, the ONFH patients showed decreased cortical thickness in the supplementary motor cortex. Consistent with this result, a study of diabetic peripheral neuropathy (DPN) with focus on painful DPN revealed impaired motor gray matter in DPN patients \(^{55}\). In addition, the duration and frequency of migraine attacks have been found to have strong effects on cortical thickness in the sensorimotor cortex \(^{56}\). The increased surface-based ReHo in the premotor cortex observed in the ONFH patients in this study might represent a compensatory increase. In our future work, we aim to explore this topic with a larger sample size. The result that ONFH patients showed significantly increased frontal eye field may indicate the abnormality of visual movement and visual attention network.

**Conclusions**

In conclusion, patients with ONFH appear to exhibit cortical and subcortical thinning and abnormal functional activity in specific brain regions associated with sensorimotor and pain processing. This is a pioneer study of the brain mechanisms in ONFH patients, as revealed by comparisons with healthy controls. There are several limitations to note. First, the sample size was small, limiting the statistical power to detect differences. Second, the different stages and types of ONFH were not considered.

**List Of Abbreviations**
**blood oxygen level dependent** | **BOLD**
---|---
diabetic peripheral neuropathy | DPN
functional connectivity | FC
magnetic resonance imaging | MRI
osteonecrosis of the femoral head | ONFH
prefrontal cortex | PFC
regional homogeneity | ReHo
regions of interest | ROI
resting-state functional magnetic resonance imaging | rs-fMRI
supplementary motor area | SMA
Total hip arthroplasty | THA
Visual Analogue Scale | VAS

**Declarations**

**Ethics approval and consent to participate**

The protocol was approved by the ethics committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine. Informed consent was obtained from all study participants.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The data sets generated and/or analyzed during this study are not publicly available because they contain protected health information. However, deidentified data sets are available from the corresponding authors on reasonable request.

**Competing Interests**

The authors declare that they have no competing of interests.

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Authors’ contributions

J.G. Xu and B. Li: study design, and data acquisition. J. Ma: drafting of manuscript. X.Y. Hua and M.X. Zheng manuscript revision. J.J. Wu and B.B. Huo conducted statistical analyses. X.X. Xing and S.Y. Feng: data collection. All authors read and approved the final manuscript.

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**Figures**

![Figure 1](image)

Comparison of surface-based ReHo values between ONFH patients and healthy controls. Compared to healthy controls, ONFH patients showed significantly increased surface-based ReHo in areas distributed mainly in the left dorsolateral prefrontal cortex and frontal eye field, the right frontal eye field and premotor cortex and decreased surface-based ReHo in the right primary motor cortex and primary sensory cortex.
Figure 2

Comparison of FC values between ONFH patients and healthy controls. When the area with decreased surface-based ReHo in the frontal eye field and right premotor cortex was used as ROI, the ONFH patients displayed increased FC in the right middle frontal cortex and right inferior parietal cortex and decreased FC in the right precentral cortex and right middle occipital cortex. Frontal_Mid_R: right middle frontal gyrus; Parietal_Inf_R: right inferior parietal gyrus; Precentral_R: right precentral gyrus; Occipital_Mid_R: right middle occipital gyrus.

Figure 3

Comparison of structural images between ONFH patients and healthy controls. a: Comparison of cortical thickness; b: Comparison of volume of subcortical gray matter nuclei. ONFH patients showed
significantly decreased cortical thickness in areas mainly distributed in the para-insular area, posterior insular area, anterior superior temporal area, frontal eye field and supplementary motor cortex. In addition, comparison of the volume of subcortical gray matter nuclei between the two groups revealed significantly decreased values in the right nucleus accumbens in ONFH patients compared with healthy controls. NAc: nucleus accumbens