Research Article

Surface-based map plasticity of brain regions related to sensory motor and pain information processing after osteonecrosis of the femoral head

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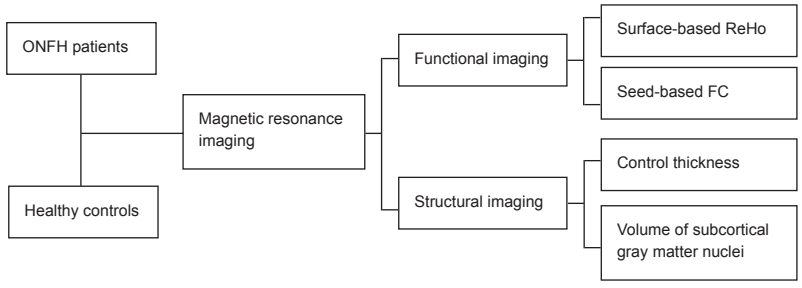
Jie Ma[1, #], Xu-Yun Hua[1, 2, 3, #], Mou-Xiong Zheng[2, #], Jia-Jia Wu[4], Bei-Bei Huo[1], Xiang-Xin Xing[1], Sheng-Yi Feng[2], Bo Li[2, *], Jian-Guang Xu[1, 4, *]

Graphical Abstract *Surface-based map plasticity in hip disorder at different levels*



Abstract

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, most studies are volume-based which may lead to inaccurate anatomical positioning of functional data. The 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. In this prospective cross-sectional study performed in Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, China, 20 patients with osteonecrosis of the femoral head (12 males and 8 females, aged 56.80 ± 13.60 years) and 20 healthy controls (9 males and 11 females, aged 54.56 ± 10.23 years) were included in this study. Data of resting-state functional magnetic resonance imaging were collected. The results revealed that compared with healthy controls, compared with the healthy controls, patients with osteonecrosis of the femoral head (ONFH) showed significantly increased surface-based regional homogeneity (ReHo) in areas distributed mainly in the left dorsolateral prefrontal cortex, frontal eye field, right frontal eye field, and the premotor cortex and decreased surface-based ReHo in the right primary motor cortex and primary sensory cortex. Regions showing significant differences in surface-based ReHo values between the healthy controls and patients with ONFH were defined as the regions of interests. Seed-based functional connectivity was performed to investigate interregional functional synchronization. When the areas with decreased surface-based ReHo in the frontal eye field and right premotor cortex were used as the regions of interest, compared with the healthy controls, the patients with ONFH displayed increased functional connectivity in the right middle frontal cortex and right inferior parietal cortex and decreased functional connectivity in the right precentral cortex and right middle occipital cortex. Compared with healthy controls, patients with ONFH showed significantly decreased cortical thickness in the para-insular area, posterior insular area, anterior superior temporal area, frontal eye field and supplementary motor cortex and reduced volume of subcortical gray matter nuclei in the right nucleus accumbens. These findings suggest that hip disorder patients showed cortical plasticity changes, mainly in sensorimotor- and pain-related regions. This study was approved by the Medical Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (approval No. 2018-041) on August 1, 2018.

Key Words: cortical thickness; functional connectivity; hip disorder; osteonecrosis of the femoral head; ReHo; sensorimotor cortex; surface-based map plasticity; volume of subcortical gray matter nuclei

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[1]School of Rehabilitation Science, Shanghai University of Traditional Chinese Medicine, Shanghai, China; [2]Department of Traumatology and Orthopedics, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China; [3]Yangzhi Rehabilitation Hospital (Shanghai Sunshine Rehabilitation Center), Tongji University, Shanghai, China; [4]Center of Rehabilitation Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

*__Correspondence to:__ Jian-Guang Xu, MD, PhD, xjg@shutcm.edu.cn; Bo Li, MD, PhD, libo@shyueyanghospital.com.

https://orcid.org/0000-0003-0601-3403 (Jian-Guang Xu); 0000-0002-3063-6312 (Bo Li)

#These authors contributed equally to this work.

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Introduction

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. ONFH is a progressive pathological process characterized by ischemia, necrosis, and eventually collapse. 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 (Feng et al., 2020). Prolonged and chronic pain can both alter neural plasticity at the cortical level (May, 2008). It has gradually been recognized that cerebral processes contribute to pain beyond the level of nociceptive input and contact behavioral and psychological influences (Woo et al., 2017). Pain is a complex sensory and emotional experience that is shaped by psychobiology, expectations from past and learned pain experiences and attention processes (Morton et al., 2016). Current theories describe the brain activity of pain as abnormal functioning in large-scale networks that include non-nociceptive regions (Farmer et al., 2012; Kucyi and Davis, 2015).

The remodeling of somatosensory cortex evidences the plasticity of the somatotopic map (Feldman and Brecht, 2005). Recently, somatosensory cortex stimulation has been proposed as a possible treatment for deafferentation pain after amputation (De Ridder et al., 2013). Exploring the map plasticity in patients with ONFH can provide insight into its possible treatment. Therefore, based on previous studies which have discovered abnormal brain activity in many kinds of diseases related to sensory abnormality (Hedera, 2012; Wang et al., 2020), 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 (Hellier et al., 2003; Tucholka et al., 2012), and it is difficult to account for inter-subject variability in gyrus size, shape or position in a three-dimensional display; furthermore, such differences may correspond to the displacement of a functional focus to a different gyrus in some subjects (Tucholka et al., 2012). As a large part of the data originates from the cortex, the 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.

Resting-state functional magnetic resonance imaging (fMRI), as a convenient and noninvasive method, has been widely used in the evaluation of central remodeling in various diseases related to pain (Emmert et al., 2017; Lin et al., 2021). 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) (Zang et al., 2004) and seed-based functional connectivity (FC) (Greicius et al., 2003) were chosen to analyze localized and remote changes in brain functions. Compared with three-dimensional ReHo, surface-based ReHo has higher test-retest reliability and can more clearly reveal the intrinsic functional organization of the cortex (Jiang and Zuo, 2016), which could be extremely useful for integrating various measures of both the structure and function of the cortical surface (Zuo et al., 2013). Cortical thickness and the volume of subcortical gray nuclei were also analyzed in the study.

Participants and Methods

Participants

This is a cross-sectional study which was performed at the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, China. Twenty right-handed ONFH inpatients without receiving surgery (12 males and 8 females, aged 56.80 ± 13.60 years) who were consecutively recruited and 20 right-handed healthy controls (9 males and 11 females, aged 54.56 ± 10.23 years) were enrolled in this study. ONFH was diagnosed according to magnetic resonance imaging (MRI) findings and clinical manifestations (Feng et al., 2020). Patients were included if they had joint pains in groin, buttock and thigh areas and Visual Analogue Scale scores for pain (Dworkin et al., 2005) ≥ 4 over 1 year. Among them, ONFH occurred on the left side in five patients, on the right side in five patients, and in both sides in 10 patients. The healthy controls were included if their Visual Analogue Scale (VAS) scores were 0 without pain related diseases and they had no abnormal findings on conventional brain MRI, such as infarction or focal lesion. Individuals (18–80 years) were excluded from the study if they had a history of cardiovascular disease, ankylosing spondylitis, rheumatoid arthritis, hip dysplasia, metabolic disorders, or bone tumor. This study was approved by the Medical Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (approval No. 2018-041) on August 1, 2018. Informed consent was obtained from all participants included in this study. This study was conducted in accordance with the ethical principles of the *Declaration of Helsinki*. There were no significant differences in education and operation history between ONFH patients and healthy controls. The study flow chart is shown in **Figure 1**.

MRI data acquisition

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

Functional imaging

Resting-state fMRI data were obtained with eyes closed and a single-pass gradient recalled (echo-planar imaging) EPI sequence with the following protocols: interleaved scanning order, slice number = 43, flip angle = 90°, matrix size = 64 × 64, repetition time (TR) = 3000 ms, slice thickness = 3.0 mm, field of view = 230 × 230 mm^2, gap = 0 (voxel size 3.6 × 3.6 × 3.0 mm^3), and number of acquisitions = 200.

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°, field of view = 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 (DPARSurf V4.3) (Yan et al., 2016), which is based on Statistical Parametric Mapping (SPM12) (http://www.fil.ion.ucl.ac.uk/spm), on a MATLAB 2013b platform (The Mathworks Inc., Natick, MA, USA). Preprocessing was performed as previously reported (Li et al., 2014). (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), and two participants (healthy controls) were excluded; (3) spatial normalization; (4) regression of nuisance variables (the white matter and cerebral spinal fluid blood oxygen level dependent 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 (full-width at half-maximum = 6 mm) was performed after surface-based ReHo calculation as previous study (Li et al., 2014). Regions showing significant differences in surface-based ReHo values between the two groups were defined as regions of interest (ROIs) for seed-based FC analysis to investigate interregional functional synchronization. FC calculation was performed as a previous study (Chen et al., 2019): (1) ROIs were extracted using REST toolbox (Song et al., 2011) based on MATLAB 2013b platform. According to the results, the left dorsolateral prefrontal cortex (PFC) and frontal eye field, the right frontal eye field and premotor cortex, the right primary motor cortex and primary sensory cortex were chosen as the ROIs for further analysis. (2) The mean time course was extracted for each ROI and correlated with time series of each voxel over the whole brain for each subject. (3) A Fisher r-to-z transformation was used to improve normality.

Statistical analysis

Two-sample *t*-test was performed by using SPSS 21.0, statistical software (IBM Corporation, Armonk, NY, USA) 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*-test was used to analyze surface-based ReHo and cortical thickness differences between the ONFH patients and healthy controls. The results were corrected for multiple comparisons, a more strict threshold ($P < 0.01$, cluster size > 50 voxels) was used for each cohort to reduce the possibility of false negative results. Two-sample *t*-test was used to analyze FC differences between the ONFH patients and healthy controls. We employed a cluster-level family-wise error correction for multiple comparisons ($P < 0.05$).

The essence of fMRI image is digit, and fMRI data are measurement data. We planned a study of a continuous variable from independent control subjects (healthy controls) and patients (ONFH). Considering a true difference in the experimental and control means of 0.07 in ReHo according to our pre-test, we performed the sample size estimation and found that at least 18 experimental subjects and 18 control subjects should be enrolled to reject the null hypothesis that the population means of the experimental and control were equal with probability (power) of 0.80. The type I error probability associated with this test of this null hypothesis was 0.05 (α) (Bacchetti and Leung, 2002).

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 PFC 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 ($P < 0.01$; **Figure 2** 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 3** and **Table 2**, when the areas with decreased surface-based ReHo in the right frontal eye field and premotor cortex were used as ROIs, 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. FC values of another two ROIs did not significantly differ between the two groups ($P < 0.05$, FWE corrected).

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 ($P < 0.01$). 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 4** and **Table 3**).

Table 1 | **Surface-based regional homogeneity values in patients with osteonecrosis of the femoral head *versus* healthy controls**

Overlap of atlas region	Hemisphere	Cluster size	Cluster centroid Montreal Neurological Institute coordinates			Peak *t*-value
			X	*Y*	*Z*	
42.86% dorsolateral prefrontal cortex (9–46 d) 28.57% frontal eye field (8Ad) 28.57% dorsolateral prefrontal cortex (9p)	Left	55.62	6.28	79.5	28.1	3.66
88.89% frontal eye field (8Av) 11.11% premotor cortex and frontal eye field (i6–8)	Right	67.25	6.28	52.78	38.68	4.09
95% primary sensory cortex (3a,3b) 5% primary motor cortex (4)	Right	56.91	–14.74	–12.42	70.83	–4.01

Table 2 | **Functional connectivity values in patients with osteonecrosis of the femoral head *versus* healthy controls**

Region label	Cluster size	Cluster centroid Montreal Neurological Institute 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	–6.9

Table 3 | Cortical thickness in patients with osteonecrosis of the femoral head *versus* healthy controls

Overlap of atlas region	Hemisphere	Cluster size	Cluster centroid Montreal Neurological Institute coordinates			Peak *t*-value
			X	*Y*	*Z*	
64.89% para-insular area	Right	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 (s6–8)	Right	67.69	–19.3	54.03	53.8	–4.14
29.35% supplementary motor cortex (6ma)						

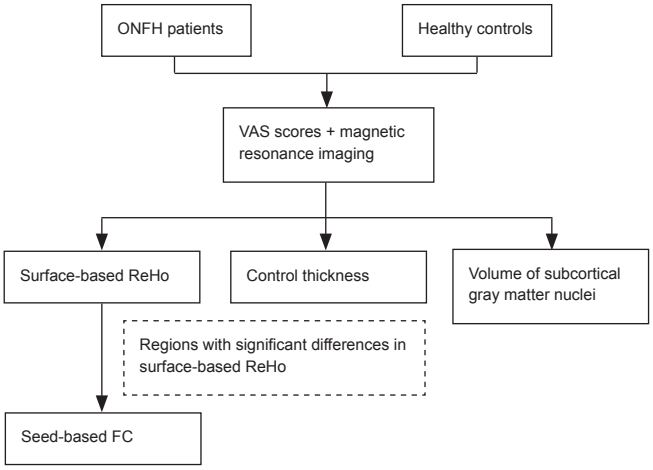

Figure 1 | Study flow chart.
FC: Functional connectivity; ONFH: osteonecrosis of the femoral head; ReHo: regional homogeneity; VAS: visual analogue scale.

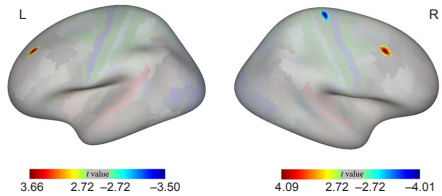

Figure 2 | Comparison of surface-based ReHo values between ONFH patients and healthy controls.
Compared to healthy controls, ONFH patients showed significantly increased surface-based ReHo in areas distributed mainly in the left dorsolateral prefrontal cortex and frontal eye field, the right frontal eye field and premotor cortex and decreased surface-based ReHo in the right primary motor cortex and primary sensory cortex. L: Left; ONFH: osteonecrosis of the femoral head; R: right; ReHo: regional homogeneity.

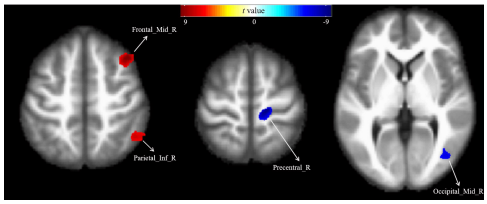

Figure 3 | Comparison of FC values between ONFH patients and healthy controls.
When the areas with decreased surface-based regional homogeneity in the frontal eye field and right premotor cortex were used as regions of interest, ONFH patients displayed increased FC in the right middle frontal cortex (Frontal_Mid_R) and right inferior parietal cortex (Parietal_Inf_R) (marked with red) and decreased FC in the right precentral cortex (Precentral_R) and right middle occipital cortex (Occipital_Mid_R) (marked with blue). FC: Functional connectivity; ONFH: osteonecrosis of the femoral head.

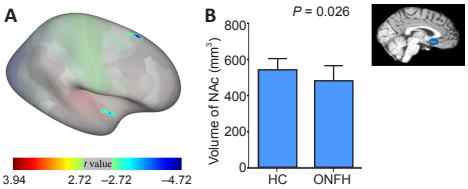

Figure 4 | Structural images of ONFH patients and HC.
(A) Comparison of cortical thickness. ONFH patients showed significantly decreased cortical thickness in areas mainly distributed in the para-insular area, posterior insular area, anterior superior temporal area, frontal eye field and supplementary motor cortex. (B) Comparison of volume of subcortical gray matter nuclei. The volume of subcortical gray matter nuclei in the right nucleus accumbens of ONFH patients was significantly decreased compared with HC. Data are expressed as mean ± SD (n = 20) and were analyzed by two-sample t-tests. HC: Healthy controls; ONFH: osteonecrosis of the femoral head.

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 PFC, 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 (Microsurgery Department of the Orthopedics Branch of the Chinese Medical Doctor Association et al., 2017). There are two complementary pathways related to pain processing: the medial and lateral pain pathways (Bowsher, 1957). In the present study, ONFH patients showed a functional decline in the primary sensory cortex, which is compatible with the existence of complementary pathway related to pain processing and aligns with the results of brain function studies in other non-central nervous system diseases with pain (Mykland et al., 2019; Sandström et al., 2019). Interestingly, both of these pathways involve the insular cortex. In pain matrix, 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 (Kim et al., 2020). 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 (Woodworth et al., 2019; Lai et al., 2020; Li et al., 2020). Usui et al. (2020) reported 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 (Ushirozako et al., 2019) and fibromyalgia (Usui et al., 2020). We also observed that the volume of the nucleus accumbens was significantly decreased

in ONFH patients compared with the healthy controls. Makary et al. (2020) provided evidence that a lower nucleus accumbens volume confers a 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 (Apkarian et al., 2005; Baliki et al., 2012). Increased activation of the PFC is related to decreased pain and inhibits the FC between the midbrain and the medial thalamus (Morton et al., 2016). 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 (Brown and Jones, 2010). Neuroimaging studies indicate that upregulation and downregulation of negative emotions are associated with increased activation of prefrontal regions (Buhle et al., 2014). These observations demonstrate that the PFC plays an important role in pain processing (Jones et al., 2012). We found that ONFH patients showed significantly increased ReHo in the dorsolateral PFC. Notably, the areas with significantly increased ReHo are in the central part of the PFC. The dorsolateral PFC is functionally linked to the descending pain modulation system and has been implicated in top-down pain inhibition, including placebo analgesia (Hibi et al., 2020). 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 PFC (Sawada et al., 2020). Similarly, during pain onset, a higher blood oxygen level dependent signal response in the dorsolateral prefrontal cortices was observed in fibromyalgia patients than in control subjects (Hubbard et al., 2020). Therefore, brain hyperactivation may be a mechanism underlying the generalized hypervigilance to salient stimuli in pain (Hubbard et al., 2020).

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 (Chenji et al., 2016). The FC analysis revealed differences in sensorimotor regions between ONFH patients and healthy controls. These findings are consistent with a previous pain study that showed abnormal FC of sensorimotor cortex in primary dysmenorrhea patients (Han et al., 2019). Furthermore, some studies have confirmed a relationship between pain persistence and aberrant sensorimotor cortex activity (Jenkins et al., 2019). 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 with focus on painful diabetic peripheral neuropathy revealed impaired motor gray matter in diabetic peripheral neuropathy patients (Zhang et al., 2020). In addition, the duration and frequency of migraine attacks have been found to have strong effects on cortical thickness in the sensorimotor cortex (Magon et al., 2019). The increased surface-based ReHo in the premotor cortex observed in 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.

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.

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Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms from the patients. In the forms, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.*
Reporting statement: *This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.*
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P-reviewers: Gaudin XP, Dimitriadis SI; S-Editors: Yu J, Li CH; L-Editors: Song LP; T-Editor: Jai Y