Observational Study

High-order Brain Networks Abnormalities in Osteonecrosis of the Femoral Head Patients: An Independent Component Analysis of Resting-state fMRI

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Background: Patients with osteonecrosis of the femoral head commonly present with sensorimotor anomalies. With independent component analysis, it is possible to explore the intrinsic alternations in highly specific functional networks. We used independent component analysis to examine the intrinsic changes and interactive connectivity between related functional resting-state networks.

Objective: The purpose of this study was to strengthen the theoretical basis of brain plasticity after osteonecrosis of the femoral head to provide new insights into clinical treatment.

Study Design: Observational study.

Setting: School of rehabilitation science of a university.

Methods: Functional magnetic resonance imaging data were acquired from 14 patients with osteonecrosis of the femoral head and 20 healthy controls. All the data underwent preprocessing and analysis of the intrinsic brain functional connectivity within and between resting-state networks.

Results: Nine resting-state networks were identified via independent component analysis. When compared to healthy controls, the osteonecrosis of the femoral head patients showed abnormal activity in these networks. With respect to the internetwork interactions, increased functional connectivity was detected between the sensorimotor network and right frontoparietal network and between the dorsal attention network and frontoparietal network bilaterally.

Limitations: This study was a cross-sectional design. A longitudinal study of the dynamic changes in multinetwork functional connectivity can help to elucidate the central mechanisms of osteonecrosis of the femoral head.

Conclusions: This study investigated the alterations in resting-state network functional connectivity in osteonecrosis of the femoral head patients. Examining the large-scale functional reorganization in osteonecrosis of the femoral head patients may be helpful for us to understand the pathological mechanisms underlying dysfunction and shed light on potential behavioral treatments for osteonecrosis of the femoral head based on functional magnetic resonance imaging in clinical practice. Understanding the mechanisms of the disease may shed light on potential behavioral treatments for patients with osteonecrosis of the femoral head based on functional magnetic resonance imaging findings.

Key words: fMRI, pain, osteonecrosis of the femoral head, functional connectivity, independent component analysis

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Osteonecrosis of the femoral head (ONFH) is a common orthopedic disease accompanied by a high disability rate that affects more than 20 million people worldwide (1,2). ONFH is characterized by an interruption of the blood supply to the femoral head, which may cause progressive osteocyte and bone marrow necrosis (3). Previous studies have thoroughly explained the pathophysiology of ONFH and divided ONFH into traumatic and nontraumatic ONFH (4). However, according to the literature, both traumatic ONFH, which is caused by femoral head and neck fracture, hip sprain, contusion and dislocation, and acetabular fracture, and nontraumatic ONFH, which is caused by steroids, chronic heavy alcoholism, smoking, obesity, and autoimmune diseases, lead to an interruption of blood supply. Glucocorticoids, for example, are known to lead to intravascular occlusion from thrombosis, lipid deposition in extravascular bone marrow, and damage to endothelial cells, inducing ONFH (5,6). Patients with ONFH frequently suffer from pain, stiffness, limitation of mobility, atrophy of lower extremity musculature with longer standing disease, and instability. Unfortunately, the cause of osteonecrosis is not always apparent, which limits effective preventative treatment in some patients (7). In Ohzono's study (8), greater than 70% of untreated patients progressed to develop severe hip degeneration and femoral head collapse, ultimately requiring a total hip replacement (THR). THR is not optimal for patients younger than 50 years old due to the current 25-year limited longevity of prostheses (9). Numerous treatments have been developed to prevent or delay disease progression, including core decompression and free vascularized fibular grafting (10,11). These treatments cannot always recover the patient's full hip joint function or eliminate hip pain in the long term. Therefore, treatment for patients with ONFH may be improved by understanding the associated central remodeling of the brain that can occur with the various factors that lead to ONFH. With advances in magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), more attention has been given to the physical and functional brain changes associated with the disease. Hadjigeorgiou et al (12) found that cerebral white matter lesions were significantly increased in patients with ONFH. Davis and Moayedi's study (13) demonstrated gray matter volume loss in patients suffering from osteoarthritis. Other research has inferred that the long-term pain of arthritis could alter brain circuitry, leading to cognitive deficits and emotional disorders (14,15). Therefore, we believe that it is necessary to study ONFH from the perspective of central remodeling.

Modern fMRI has provided an effective method for measuring functional changes in the brain. fMRI is a four-dimensional imaging approach and is the only effective, noninvasive technique for measuring brain activation in human beings (16). fMRI is commonly used as an investigational tool in the study of abnormal intrinsic activity (17). fMRI is valuable for planning therapeutic interventions and determining a prognosis after disease and injury (18). Recent fMRI studies of brain function have shown that it is possible to identify a variety of highly specific functional networks that account for a significant portion of intrinsic activity (19,20). Independent component analysis (ICA) is an efficient method for exploring intrinsic alternations in brain functional subnetworks (19). As a blind source separation method, ICA can recover a set of signals from their linear mixture and has yielded fruitful results with fMRI data (21). Spatial ICA separates fMRI data into a set of maximally spatially independent maps and their corresponding time courses. The dynamics of the blood oxygen level dependent (BOLD) signal within a single component is described by that component's time course in resting-state fMRI data. The regions contributing significantly within a given component are strongly functionally connected to each other. This kind of biological relevance is known as a resting-state network (RSN) (22). RSNs are used as a robust brain mapping tool for evaluating regional interactions occurring in a resting or task-negative state. RSNs are used because of their high reproducibility and moderate to high test-retest reliability.

In this study, we used ICA to evaluate intrinsic changes and interactive connectivity between related functional subbrain networks. Our results strengthen the theoretical basis for brain plasticity after ONFH.

Methods

Patients

Seventeen right-handed patients with right ONFH and 23 healthy, right-handed control patients were recruited in this study. The inclusion criteria for participation were that the patients ages ranged from 18 to 80 years and had ONFH stages in compliance with the Association Research Circulation Osseous (ARCO) classification (23). Patients who met any of the following criteria were excluded from the study: current or

previous inflammatory arthritis or other diseases of the hip joint, skeletal immaturity, serious cardiovascular disease, hepatic or renal disease, a history of hip joint surgery, still on corticosteroid therapy, pregnant or lactating women, malignant disease, serious current infection or hematological disease, and neuropsychiatric disease. This study was approved by the Ethics Review Board of Yueyang Hospital of Integrated Chinese and Western Medicine affiliated with Shanghai University of Chinese Medicine and was conducted according to the guidelines of the Declaration of Helsinki. Each participant was fully informed and signed a consent form before the study.

Data Acquisition

The fMRI data were acquired on a Magnetom Trio A 3T MR Scanner (Siemens AG, Erlangen, Germany). During the resting-state fMRI session, the patients were instructed to relax with their eyes closed and keep their heads still during the scans. Functional images were subsequently acquired with the same slice orientation with an EPI (gradient recalled echo, echo-planar imaging) sequence (TR/TE = 3,000 ms/30 ms, FOV = 24.0 × 24.0 cm^2, flip angle = 90°, matrix = 64 × 64, slice thickness = 3.0 mm, slice gap = 0.4 mm, 43 slices, number of acquisitions = 200, acquisition voxel size = 3.6 × 3.6 × 3.0 mm).

fMRI Data Preprocessing

AN SPM (statistical parametric mapping)-based fMRI data processing pipeline, RESTplus (http://rest-fmri.net/forum/RESTplusV1.2), was used to perform the data preprocessing, including removing the first 10 volumes, slice-time correction, realigning head motion correction, normalizing to EPI standard templates and resampling to 3.0 × 3.0 × 3.0 mm^3, smoothing using a 6-mm FWHM isotropic Gaussian kernel, and excluding movement more than 2.0 mm or rotation that exceeded 2.0°. Temporal bandpass filtering (0.01 – 0.08 Hz) was used to decrease the low-frequency drift.

Analysis of Intrinsic Brain Functional Connectivity within RSNs (RS FC analysis)

The independent components (ICs) for all the patients were analyzed by GIG-ICA (GIFT software; https://www.nitrc.org/projects/gift, version 4.0a). The procedures using this toolbox include 3 steps: first, dimension reduction; second, applying the ICA informax algorithm; and third, back reconstruction for individual level components. Finally, 43 ICs were autoestimated through the minimum description length (MDL) criteria, and GIG-ICA was performed 100 times. Nine meaningful RSNs were identified as anatomically and functionally classic RSNs via visual inspection.

A threshold for each IC was established using a random-effect, one-sample t-test with a false discovery rate (FDR) correction ($P < 0.05$) to remove atypical voxels with small correlation coefficients and retain highly correlated voxels. The mean time course was calculated by averaging the time courses within each RSN mask obtained from the ICA processing. Pearson correlation coefficients of the mean time courses between each pair of RSNs for individual patients were calculated. Then a Fisher's z transformations was performed to improve normality.

The next step was to determine whether the correlation between each pair of RSNs in each group was statistically significant. Each patient's z values were introduced in a one-sample t-test ($P < 0.05$). The intranetwork functional connectivity (FC) differences in all RSNs among the ONFH patients were extracted, and the healthy controls were tested using general linear model (GLM) analysis with age and gender as covariates (uncorrected voxel P value < 0.001).

Analysis of Functional Network Connectivity Between the RSNs (FNC analysis)

FC refers to the neurophysiological relationship between spatially separated brain regions and reflects whether there is a connection or interaction between 2 brain functional areas. Intergroup comparisons were performed using the GLM to explore whether pairs of internetwork FC were significantly different between the ONFH patients and healthy controls. The FNC toolbox was used to examined the temporal correlation between the identified networks (http://trendscenter.org/software/). For the significant correlation combinations, the average time lags, which reflected the interdependency of 2 subbrain networks, were used to calculate the delay between the 2 networks. The maximal correlation coefficient was obtained by setting the time lag to 6 seconds. Two-sample t-tests ($P < 0.05$) for group comparisons were applied to all possible combinations.

Results

Patient Characteristics

After checking the head motion, the final cohort in this study consisted of 14 ONFH patients and 20 healthy patients. No significant differences in gender

or age were found between the patients and control patients ($P > 0.05$). The demographics and clinical data for both the ONFH patients and healthy controls are listed in Table 1.

Identification of RSNs for HC and ONFH

A total of 43 components were estimated through ICA. Nine meaningful RSNs were extracted from all the patients (Fig. 1), including the posterior default mode network (pDMN), auditory network (AN), dorsal visual network (dVN), medial visual network (mVN), sensorimotor network (SMN), right frontoparietal network (RFPN), left frontoparietal network (LFPN), dorsal attention network (DAN), and ventral attention network (VAN).

Group Comparisons of Activity in RSNs

Compared with the healthy controls, the patients showed significant activity differences in multiple RSNs (Table 2). For the SMN, the activity decreased in the left precentral and inferior orbitofrontal gyri and increased in the right postcentral and left inferior parietal gyri. In the pDMN, the activity decreased in the right superior parietal gyrus and the left orbital superior frontal gyrus. In the RFPN, the activity decreased in the left middle occipital gyrus and the right inferior temporal gyrus. In the LFPN, the activity increased in the right superior medial frontal gyrus and decreased in the left precuneus, right superior temporal, and bilateral medial superior frontal areas. In the VAN, the activity decreased in the right middle temporal gyrus and rolandic operculum. In the DAN, the activity increased in the left middle occipital and superior medial frontal gyri and decreased in the left inferior frontal gyrus. In the AN, the activity decreased in the right supplementary motor area and left middle occipital gyrus and increased in the right precentral and superior temporal gyri and left thalamus.

Table 1. *Demographic information of the patients, the dataset include 34 patients (16 men) with age range 26-78 years old.*

	Patients	ONFH	HC	*P* value
	34	14	20	
Gender (Men)	16	8	8	0.075
Age (years)				0.339
Mean	48.3	55.07	43.70	
SD	18.3	15.8	18.9	

ONFH: Osteonecrosis of the femoral head; HC: Healthy control.

Group Comparisons of FC between RSNs

The level that determined significant differences in the RSN correlations between the 2 groups was set to $P < 0.05$. Compared with the healthy controls, the ONFH patients exhibited significantly increased FC between the SMN and RFPN, the DAN and RFPN, and the DAN and LFPN (corrected, $P < 0.05$). The results of FNC analysis are shown in Fig. 2.

Discussion

The primary aim of the present study was to clarify the neural mechanisms underlying ONFH in patients based on resting-state ICA. This study investigated the intrinsic FC within/between brain subnetworks, which is known to be involved in higher-order cognition and sensorimotor tasks. We found that the intranetwork activity within the SMN, DAN, RFPN, and LFPN was mainly decreased in ONFH patients. These results were similar to other fMRI studies in joints (14,24). The internetwork FCs between the SMN and RFPN, RFPN and DAN, and LFPN and DAN were increased in the ONFH patients. The results indicated that ONFH might lead to abnormal FC between and within RSNs.

The SMN consists of the precentral, postcentral, and medial frontal gyri, the primary sensory-motor cortices, and the supplementary motor area. The SMN contributes to sensorimotor integration during motor execution and sensory feedback (25). The lower limb is essential for standing and walking; Kapreli et al (26) demonstrated that lower limb movements changed the activity pattern of the SMN. Thaploo et al (27) suggested that the persistent discomfort caused by impaired joints is recognized by the central nervous system and creates negative feedback to adjust the limb to the most comfortable position to avoid undesirable sensations of pressure. This phenomenon is similar to functional impairment in brachial plexus avulsion injury, and dysfunction of lower limbs in ONFH patients also caused abnormal activity of SMN (27). In our experiment, we found that FC decreased in the left precentral gyri and increased in the right postcentral gyri in right ONFH patients compared to normal controls, suggesting an abnormal SMN.

For internetwork comparisons, FC between the SMN and the RFPN increased in ONFH patients. The RFPN consists of the right middle frontal gyrus, inferior parietal lobule, superior parietal lobule, and angular gyrus (28). The RFPN is involved in cognitive control and top-down modulation, and it is recognized as an important brain network that corresponds to percep-

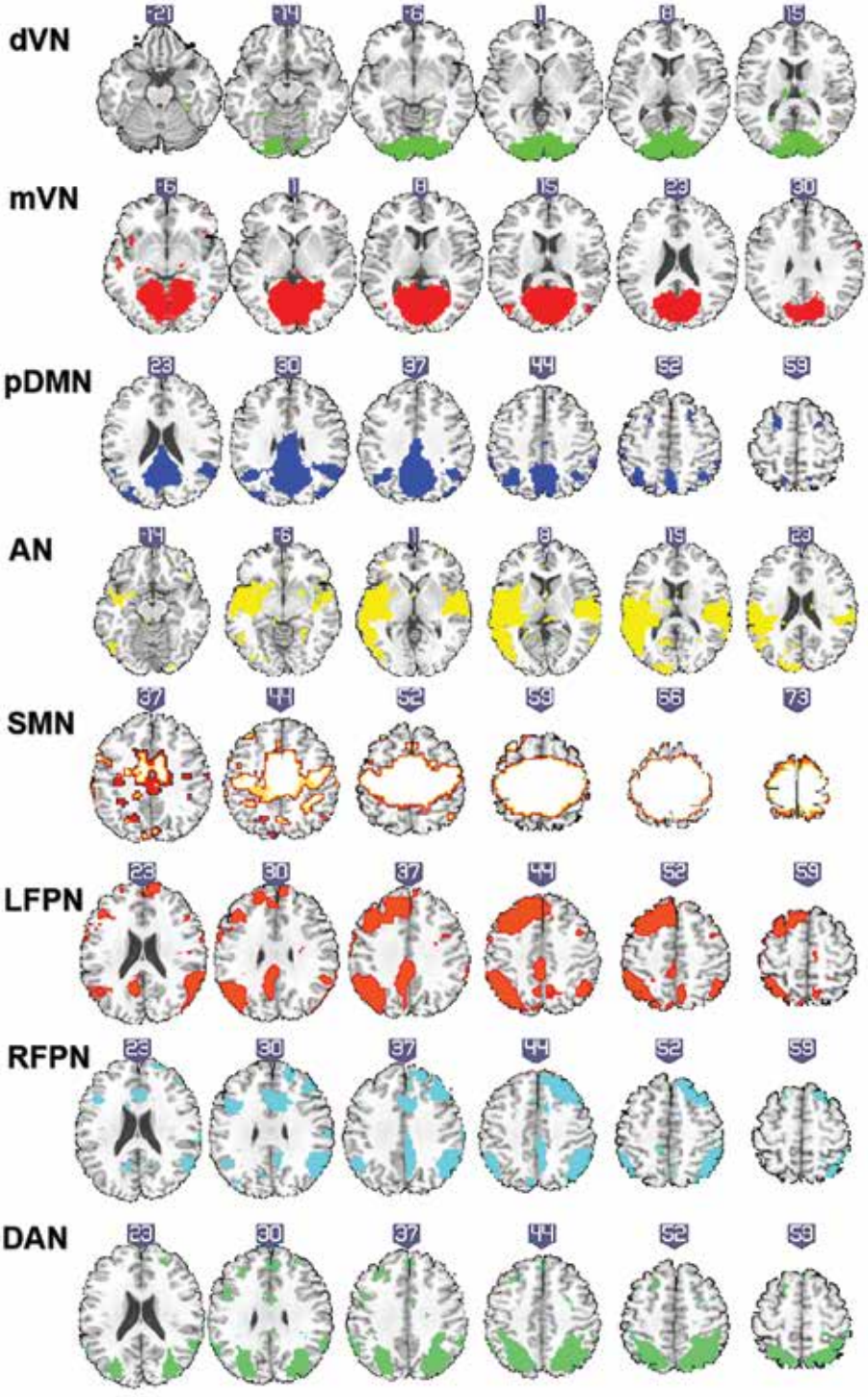

Fig. 1. *Coronal views of spatial maps for each network. The right side of the image corresponds to the right brain hemisphere.*

Table 2. *Brain regions with significant differences in intra-network functional connectivity between ONFH patients and healthy control.*

Sub-network		Region Label	Extent	t-value	MNI Coordinates		
					x	y	z
pDMN	ONFH < HC	Right Superior Parietal	15	-4.6487	21	-69	63
		Left Medial Orbitofrontal	16	-3.9914	-9	51	-3
RFPN	ONFH < HC	Left Middle Occipital	22	-5.0093	-27	-93	6
		Right Inferior Temporal	21	-3.5078	57	-18	-24
LFPN	ONFH < HC	Right Superior Medial Frontal	42	5.0797	15	60	18
	ONFH < HC	Left Precuneus	26	-3.9791	-9	-57	24
		Right Superior Temporal	21	-3.9774	63	-33	3
		Right Superior Medial Frontal	21	-3.9605	9	33	42
		Left Superior Medial Frontal	15	-3.8325	-9	45	42
VAN	ONFH < HC	Right Rolandic Operculum	35	-4.5881	54	-3	12
		Right Middle Temporal	19	-3.2746	63	-24	-6
SMN	ONFH < HC	Right Post central	13	4.5033	30	-48	69
		Left Inferior Parietal	15	3.7837	-45	-27	42
	ONFH < HC	Right Precentral	56	-4.6041	36	-12	48
		Left Inferior Orbitofrontal	19	-4.2744	-45	42	-12
DAN	ONFH < HC	Left Middle Occipital	25	5.0983	-39	-72	24
		Left Superior Medial Frontal	46	3.5685	0	39	51
	ONFH < HC	Left Inferior Frontal	25	-4.2182	-48	24	-3
AN	ONFH < HC	Right Precentral	15	4.7794	60	9	33
		Left Thalamus	17	4.4185	-15	-12	12
		Right Superior Temporal	18	3.739	57	-39	9
	ONFH < HC	Right Supplementary Motor Area	16	-4.4084	6	24	63
		Left Middle Occipital	22	-3.6546	-45	-78	6

pDMN: posterior default mode network; RFPN: right frontoparietal network; LFPN: left frontoparietal network; VAN: ventral attention network; SMN: sensorimotor network; DAN: dorsal attention network; AN: auditory network; ONFH: Osteonecrosis of the femoral head; HC: Healthy control.

tion, somesthesis, and pain (29,30). Lobanov et al (31) confirmed that the frontoparietal region played a key role in the formation and transmission of sensation that connects the primary sensory area to the secondary sensory area. Hence, there is an identified structural connection between the SMN and RFPN. Refractory and persistent pain is also a typical symptom in ONFH patients. The RFPN is strongly related to processing pain information and regulating pain. Moreover, the SMN is involved in sensory discrimination of pain processing. The postcentral gyrus receives pain signals directly. In previous studies, Seminowicz et al (32) found that the FC in the RFPN changed in patients suffering from chronic pain. Zhao et al (33) found increased FC between the RFPN and SMN in patients with persistent somatoform pain disorder. These authors speculated that this increased FC is probably caused by hyperexcitability of pain pathways, which led to disorders in high-order networks (33). Consistent across these findings, our results suggested that increased FC between the SMN and RFPN may reflect increased functional interactions between these 2 RSNs and lead to movement dysfunction and abnormal gait of the hip joint in ONFH patients. The SMN and RFPN are more likely to be parts of a circuit that processes sensory information to make a decision for action.

In addition to the SMN and RFPN, there were also increased FCs between the DAN and RFPN and the DAN and LFPN. The DAN mainly consists of the intraparietal sulcus, the frontal eye field (FEF), and the middle frontal gyrus (20). The LFPN showed similar spatial patterns to the RFPN, which consists of the left superior parietal lobule, middle frontal gyrus, and inferior parietal lobule. Studies have demonstrated that the frontopa-

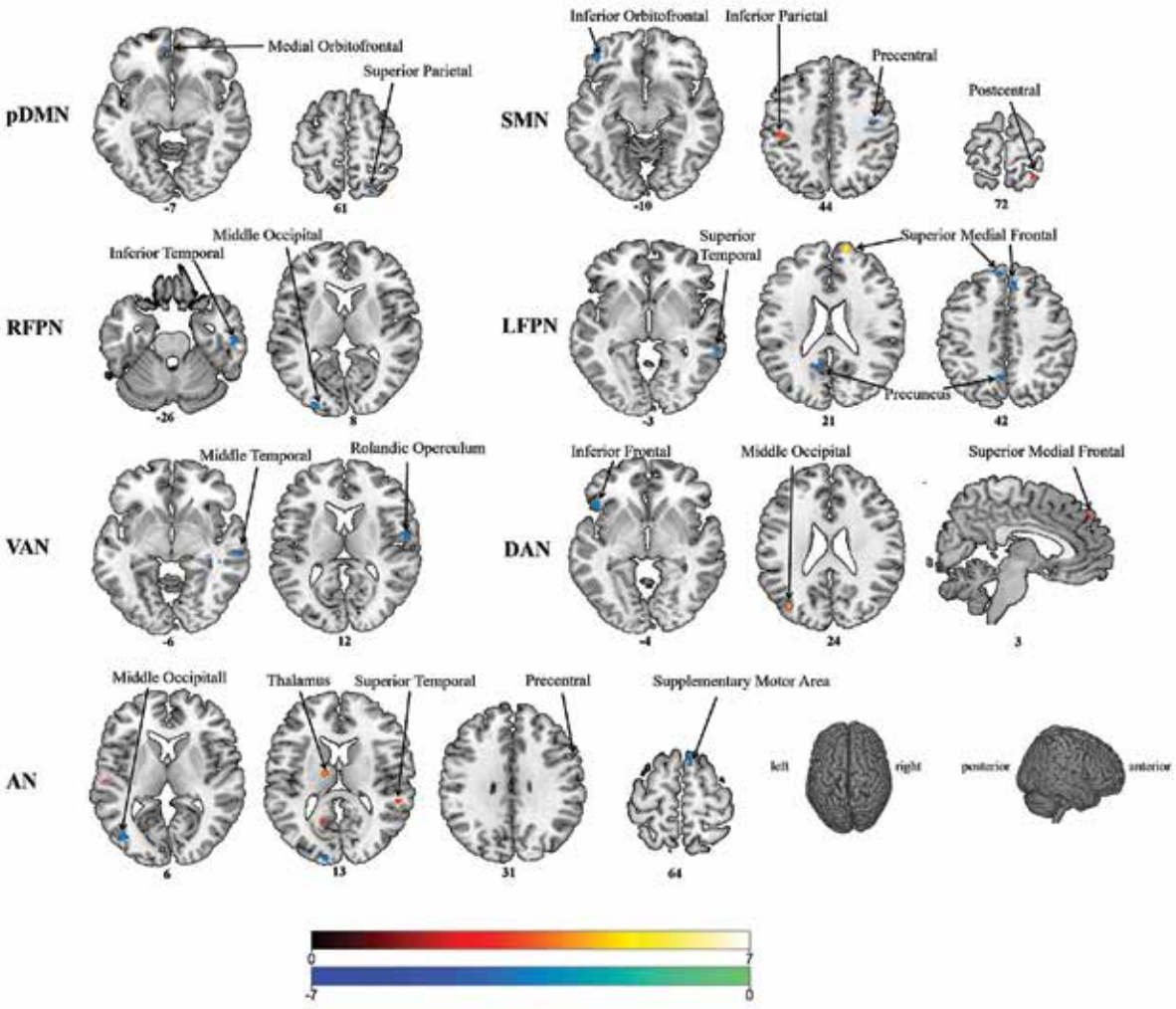

Fig. 2. *Results of RS FC analysis between the control and model groups. Altered FC in the pDMN, AN, SMN, RFPN, LFPN, DAN, and VAN. The hot (orange and yellow) colors denote higher functional activity in the model group than in the control group, and the blue color denotes lower functional activity in the model group than in the control group.*

rietal lobe is related to cognitive processing, working memory, and attention maintenance (34). It is generally accepted that the DAN and bilateral FPN are the subsystems of the frontoparietal control system (35). Dante Mantini et al (20) found that the DAN is dedicated to adaptive task control and engaged during voluntary orienting. Therefore, it plays an important role in target detection performance (22). Luckmann et al (36) thought that the DAN is a top-down modulation or biasing of these sensory processing regions that maintain, reactivate, and create internal representations of various forms of stimuli to produce different cognitive concepts. In particular, the DAN is thought to be influenced by voluntary attention shifts during searches for salient stimuli (37). Studies focused on the FPN demonstrate that the FPN primarily mediates attention, working memory, and higher order cognitive processes (38). However, unlike the cognitive performance in the RFPN, the LFPN is thought to be especially involved in highly adaptive control and language processes (28,39). All these findings may be associated with proprioception of the hip joint. The proprioception includes a sense of position and movement, effort, strength and heaviness of limbs and trunk (40). Similar to Proske

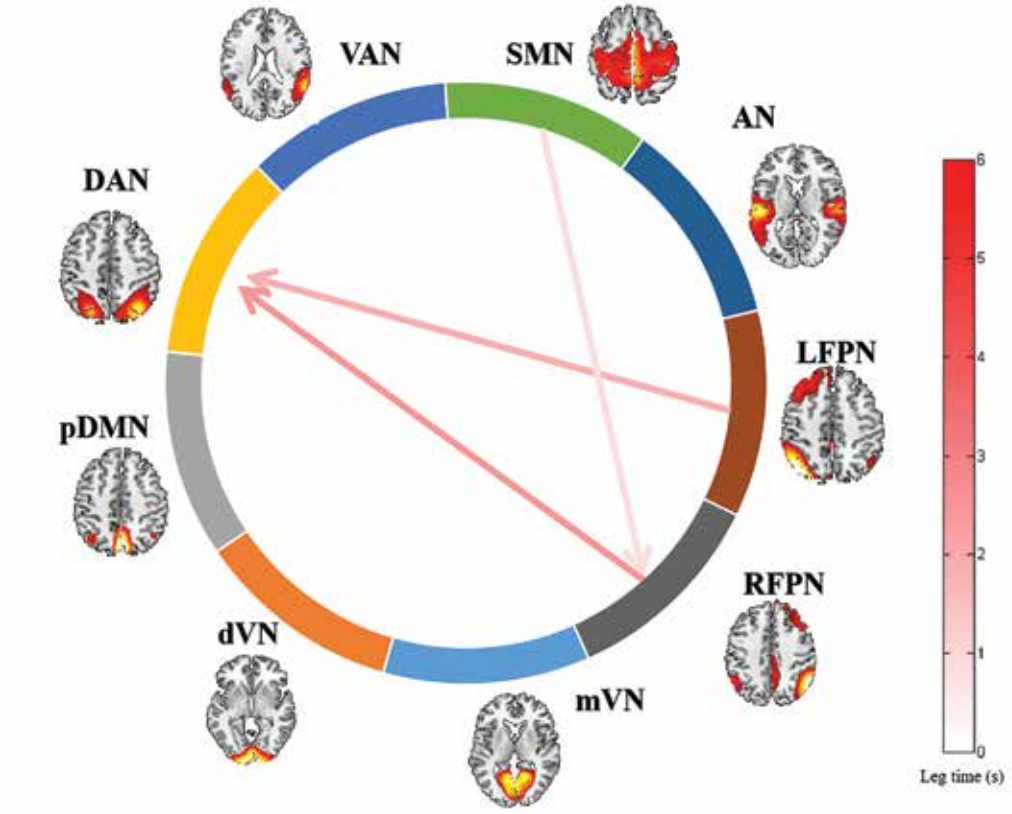

Fig. 3. *ONFH-related differences in brain functional network connectivity between subbrain networks. FNC results of the ONFH patients compared to those of the healthy controls. The color bars represent time lag (0 – 6 seconds).*

and Gandevia's study (40) about deafferented patients, ONFH patients always focus on the movement itself with visual and sensory feedback so that they can avoid uncomfortable sensations. These studies indicated that the complex brain network of the prefrontal, parietal, and temporal regions mediates attentional cognitive control, inhibitory processes, and interference control (41). This complex network could be the reason for the increased FC between the DAN and bilateral FPN.

There are limitations in this study. First, the present study was a cross-sectional design. A longitudinal study of the dynamic changes in multinetwork FC can help elucidate the central mechanisms of ONFH. Further research should focus on changes in function in multiple networks after treatment and explore whether these changes can predict long-term ONFH function. Second, our patient cohort is relatively small, and further segmentation of ONFH patients may reveal a more detailed relationship between FC patterns and symptom severity. Finally, further study can examine ONFH patients with white matter lesions.

Conclusion

The present study investigated alterations in RSN FC in ONFH patients and found significantly altered activation in the pDMN, AN, SMN, RFPN, LFPN, DAN, VAN, and FNCs between the SMN and RFPN, the LFPN and DAN, and the RFPN and DAN between ONFH patients and healthy controls. Examining the large-scale functional reorganization in ONFH patients may be helpful for understanding the pathological mechanisms underlying dysfunction and shed light on potential behavioral treatments for ONFH based on fMRI in clinical practice.

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