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Abnormal Brain Connectivity Networks in Patients with Knee Osteoarthritis: A Resting-state Functional MRI Study

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Abstract: *Background*: Resting-state functional connectivity (FC) has been nominated as an effective method for elucidating the neural mechanisms underlying chronic pain. To date, whole-brain FC alterations in chronic knee osteoarthritis (KOA) remain largely unknown. *Purpose*: To investigate the functional connectivity patterns across the entire brain in patients with knee osteoarthritis (KOA) using resting-state functional magnetic resonance imaging (rs-fMRI). *Methods*: The current rs-fMRI analysis included 56 well-characterized KOA patients and 20 healthy controls (HCs), with data obtained from OpenNeuro. To identify aberrant topological organization in the brains of KOA patients, the study employed a graph theoretical approach. Additionally, the independent component analysis was conducted to characterize both intra-network and inter-network brain connectivity in these individuals. *Results*: Both the KOA cohort and healthy control cohort exhibited small-world characteristics in brain functional networks. Additionally, compared to HCs, KOA patients showed altered global properties, specifically characterized by reduced global efficiency and increased assortativity. At the nodal level, the KOA patients exhibited decreased degree centrality and betweenness centrality in the right thalamus. Furthermore, independent component analysis indicated abnormal FC within the anterior default mode network (DMN) and salience network (SN) in this patient cohort. The inter-network interactions did not show intergroup differences after multiple-test correction. *Conclusion:* The widespread functional abnormalities observed from a whole-brain network perspective in subjects with KOA pain may provide more comprehensive insights and reinforce the grasp of the neural mechanisms underpinning KOA.

Keywords: Knee osteoarthritis; Functional connectivity; Resting-state functional MRI; Graph theory; Independent component analysis

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1. Introduction

Knee osteoarthritis (KOA) represents the most common form of joint disorder, marked by progressive deterioration and subsequent breakdown of articular cartilage [1,2], often leading to secondary damage to adjacent structures

such as bones and ligaments. Pain represents the predominant clinical manifestation of knee osteoarthritis (KOA), leading to reduced mobility and a diminished quality of life for patients [3]. Given its high prevalence, significant functional limitations, and substantial socioeconomic burden, knee osteoarthritis (KOA) has become a critical global public health concern [4–7]. Unfortunately, treatment regimens for KOA remain far from satisfactory. Limited understanding of the pathophysiological mechanisms is at least partially responsible for the experience, maintenance, and development of KOA.

Resting-state functional magnetic resonance imaging (rs-fMRI) over the past few decades has unraveled the neurophysiological processes underlying chronic pain disorders and created biomarkers related to cognitive, nociceptive, and social dimensions of pain [8–12]. A wealth of functional neuroimaging research has demonstrated that KOA exhibited significant structural remodeling and functional alterations in brain regions [13–16]. Functional connectivity (FC) denotes the temporal correlation of a neurophysiological index measured across distinct brain regions [17] and has been extensively employed in studies using rs-fMRI. However, most studies have used narrow seed-based resting-state FC approaches to analyze rs-fMRI data [13,18,19], knowledge about the functional integrity of whole-brain networks in individuals with KOA remains limited.

Analyses of rs-fMRI data, such as graph theoretical analysis and independent component analysis (ICA), have become increasingly popular for mapping brain activity, facilitating the investigation of the whole-brain network reorganization. Graph theoretical analysis views the entire brain as a complex network consisting of highly interconnected regions (referred to as nodes) that exchange bidirectional information [20–22]. This approach provides structured frameworks for measuring topological and organizational characteristics of complex networks [17,23]. In recent years, a handful of studies have tried to explore this method for analyzing rs-fMRI data of both normal and damaged human brains [24–29]. By contrast, ICA is a data-driven method to decipher spatially independent components of coherent signals, enabling hypothesis-free and observer-independent assessment of interactions within and between resting-state networks (RSNs) [30]. Chronic pain may be associated with metabolic alterations within large-scale distributed networks (e.g., default mode network, salience network, and central executive network) that comprise the pain connectome. Research into intra- and inter-network connectivity has significantly advanced our knowledge of large-scale functional organization in both healthy and disordered brains [31–33]. However, it is unclear how brain networks change in functional connectivity within and between RSNs in KOA.

Considering the aforementioned factors, our objectives were to: (1) apply graph theory methods to quantify topological differences in whole-brain networks, and (2) utilize ICA to identify distinct FC patterns within and between RSNs. The study hypothesized that: (1) the small-world attribute of the whole-brain networks in KOA would be preserved, but KOA would be characterized by abnormal topological features (both globally and locally) of functional networks compared with HCs, and (2) specific regional FC changes would be observed linked to KOA of RSNs.

2. Materials and methods

2.1. Participants

The rs-fMRI data employed in our research were acquired from OpenNeuro (https://openneuro.org/). Participants provided written informed consent sanctioned by the Northwestern University Institutional Review Board committee (STU00039556). The open sharing of rs-fMRI data includes 76 subjects, categorized into three distinct groups, and the data was initially collected to identify and validate the predictability of clinical placebo response based on rs-fMRI brain connectivity [34]. However, the data involved in our study were pre-treatment data, so these

data can be analyzed for two groups instead of four, including 20 HCs (mean age =57.90 ± 6.66 years old, 10 males and 10 females) and 56 KOA patients (mean age = 57.91 ± 6.96 years old, 26 males and 30 females). No significant differences comparing demographic variables were observed in age ($p = 0.995$) and gender ($p = 0.784$). Inclusion and exclusion criteria for all participants can be found below.

Inclusion criteria:

(1) Participants must be between 45 and 80 years old.

(2) Confirmed by ACR guidelines, with radiographic evidence (Kellgren-Lawrence grade II-IV).

(3) A visual analog scale (VAS) score exceeding 5 out of 10 within 48 hours before screening and the first visit.

(4) Symptoms must have persisted for at least one year.

(5) Daily pain relief drugs required to control osteoarthritis symptoms.

Exclusion Criteria:

(1) Use of MAO inhibitors or centrally acting drugs for pain or depression.

(2) Presence of narrow-angle glaucoma.

(3) Poorly managed hypertension.

(4) Other chronic conditions: Inflammatory arthritis, fibromyalgia, or persistent pain disorders.

(5) Females who are pregnant, attempting conception, or breastfeeding.

(6) Diagnosis of major depressive disorder.

(7) Excessive alcohol consumption or prior liver disease.

(8) Restricted medications: MAO inhibitors, triptans, serotonin precursors (e.g., tryptophan).

(9) Drug interactions: CYP1A2 inhibitors, Thioridazine, or antidepressant usage.

(10) Type 1 or type 2 diabetes.

(11) Any condition that, in the investigator's judgment, may hinder compliance, distort findings, or pose risks.

(12) MRI contraindications: Metal fragments in facial or ocular regions, or prior metalwork employment; Electronic implants (e.g., pacemakers, defibrillators, cochlear devices, neurostimulators); Prior cerebrovascular surgery; Severe claustrophobia (inability to tolerate confined spaces); Body piercings or tattoos; Weight exceeding 250 pounds; Detectable brain anomalies.

2.2. MR data acquisition

All subjects underwent MRI scanning (3T Siemens Trio whole-body) to acquire T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) structural images (repetition time: 2.5 milliseconds; echo time: 3.36 milliseconds; flip angle: 9°; voxel size: 1.00 × 1.00 × 1.00 mm; field of view: 256 mm; matrix: 256 × 256; and slices: 160. High-resolution whole-brain rs-fMRI images were acquired using a T2*-weighted echo planar imaging (EPI) sequence (repetition time: 2500 milliseconds; echo time: 30 milliseconds; flip angle: 90°; slice thickness: 3 mm; matrix: 64 × 64; number of slices: 40; and 300 volumes).

2.3. Functional data preprocessing

The rs-fMRI data were preprocessed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/) working on MATLAB R2016a. The preprocessing procedure for ICA analysis included the following stages: the first 10 volumes of each functional data set were removed to reduce equilibrium effects. The BOLD runs were subsequently corrected for slice timing and head motion. The BOLD images were spatially normalized to the Montreal Neurological Institute (MNI) standard template and resampled to 3-mm cubic voxels. Subsequently, the resulting data were smoothed by a 6-mm full-width at half-maximum Gaussian kernel. In addition to the first four steps of preprocessing for ICA,

further preprocessing for graph theory was conducted as follows: Detrending and nuisance regression procedures were applied to eliminate linear trends and non-neural-related signals, and the corrected functional images were further low-pass filtered (0.01–0.08 Hz).

2.4. Graph theoretical analyses

The whole-brain functional network construction and network metrics calculation were performed using the MATLAB-based software GRETNA toolbox (https://www.nitrc.org/projects/gretna). In topological networks, nodes and edges (FC between nodes) constitute the foundational structure. In the brain, nodes represent distinct brain regions, while edges signify the statistical relationships between BOLD signals across these regions. To define the brain nodes, a widely accepted AAL90 atlas was used to divide the entire brain into 90 cortical regions, each region representing a node within the network [35]. Pearson correlation coefficients of BOLD signals between all possible pairs of nodes were calculated to derive the brain's connectivity matrix. Individual Pearson correlation matrices were then converted using Fisher's r-to-z transformation. Finally, topological metrics of the constructed FC matrix were calculated for each subject. For this study, the study selected commonly used global network metrics, including small-world attribute (lambda, gamma and sigma), global efficiency, and assortativity, to measure the properties of global networks. For the relatively stable nodal network, local metrics included nodal efficiency, betweenness centrality, and degree centrality. The results were visualized using BrainNet Viewer [36] (https://www.nitrc.org/projects/bnv/).

To minimize bias resulting from choosing a single threshold, the study used an area under the curve (AUC) approach for each network measure. This method provides a comprehensive summary metric for assessing brain network topology and is effective in identifying topological changes associated with brain dysfunction [37,38]. Consistent with previous studies [38–40], Graph topological metrics were therefore calculated for all individual brain networks at network sparsity thresholds ranging from 0.10 to 0.34 with sparsity steps of 0.01, ensuring accurate estimation of "small-world" parameters and minimizing the inclusion of spurious edges [41–44].

2.5. Independent component analysis

Group independent component analysis (GICA) was performed using the GIFT Toolbox (https://trendscenter.org/software/gift/) . The steps for conducting group ICA and detecting intrinsic connectivity networks (ICNs) are shown as follows: the data was reduced in dimensionality through a two-step principal component analysis [45]. 50 spatially independent components was auto-estimated through the Minimum Description Length (MDL) criteria. Infomax algorithm was employed for group independent component analysis, and the process was iterated 100 times using ICASSO (http://research.ics.aalto.fi/ica/icasso/) to ensure component consistency. The time courses and spatial maps for each subject were reconstructed, followed by a Fisher Z transformation for further investigation.

2.6. Statistical analysis

Analysis of the clinical and demographic data from all participants was performed using SPSS statistics software. Group comparisons were conducted by independent 2-sample t-tests for age and chi-square tests for sex.

For graph theory analysis, 2-sample t test with multiple comparisons (FDR corrected) was conducted to compare the differences in topological properties between KOA patients and HCs, including the AUC of each global network metric and each local network metric. The significance level was set at $p < 0.05$ (control covariates: age, gender).

For independent component analysis, to compare group differences in the intra-network FC, a one-sample *t*

test ($p < 0.05$, FWE corrected) was conducted separately for KOA patients and HCs to generate sample-specific spatial pattern masks for each group. Each mask of the KOA patients and HCs was subsequently merged into a total mask for each component. Furthermore, measures of inter-network FC between KOA patients and HCs were compared using 2-sample t tests with age and sex as covariates ($p < 0.05$, FWE corrected). In addition, for inter-network FC analysis, the study derived the time-series of each RSN from the ICA procedure and calculated Pearson's correlations between pairwise combinations. To enhance normality, these values were then transformed to Z-scores. Group differences in inter-network connectivity were compared using a 2-sample t test ($p < 0.05$, FDR corrected), controlling for age and sex as nuisance covariates.

3. Results

3.1. Group comparisons of global and nodal topological properties

In the wide-defined sparsity range, the lambda values hovered at 1, both gamma and sigma exceeded 1. These findings suggest that both two groups exhibit a "small-world" organization in resting-state networks (**Figure 1A**). For the global metrics, a decreased AUC of the global efficiency ($p = 0.048$, $t = 2.01$) and an increased assortativity ($p = 0.019$, $t = -2.39$) were observed in KOA patients compared with the HCs (**Figure 1B**). For the local metrics, patients with KOA had a decreased degree centrality ($p < 0.001$, $t = 4.28$) and betweenness centrality ($p < 0.001$, $t = 4.58$) of the right thalamus (**Figure 2**).

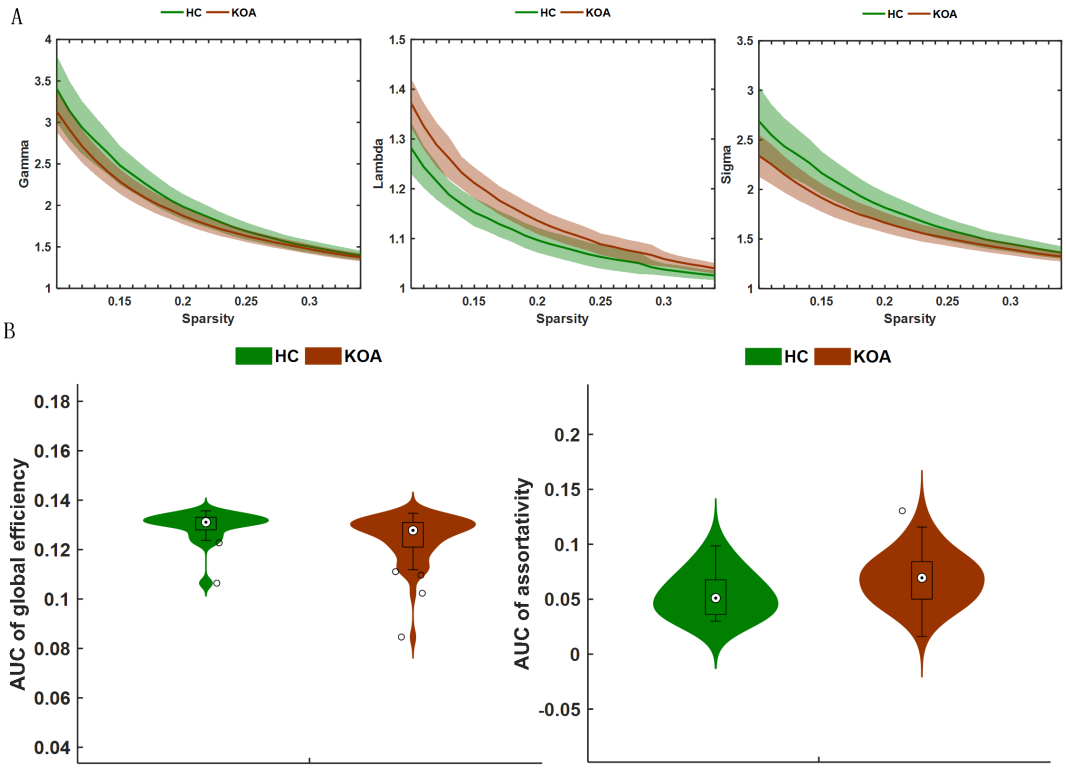

Figure 1. Group differences in global network metrics between KOA patients and HCs. (A) Small-world properties of sparsity threshold (10%-34%, with a step of 1%). The line and shading show the mean and 95% confidence interval of between-group differences. (B) Violin plots illustrating the area under the curve (AUC) parameters of the global efficiency and assortativity for KOA patients and HCs.

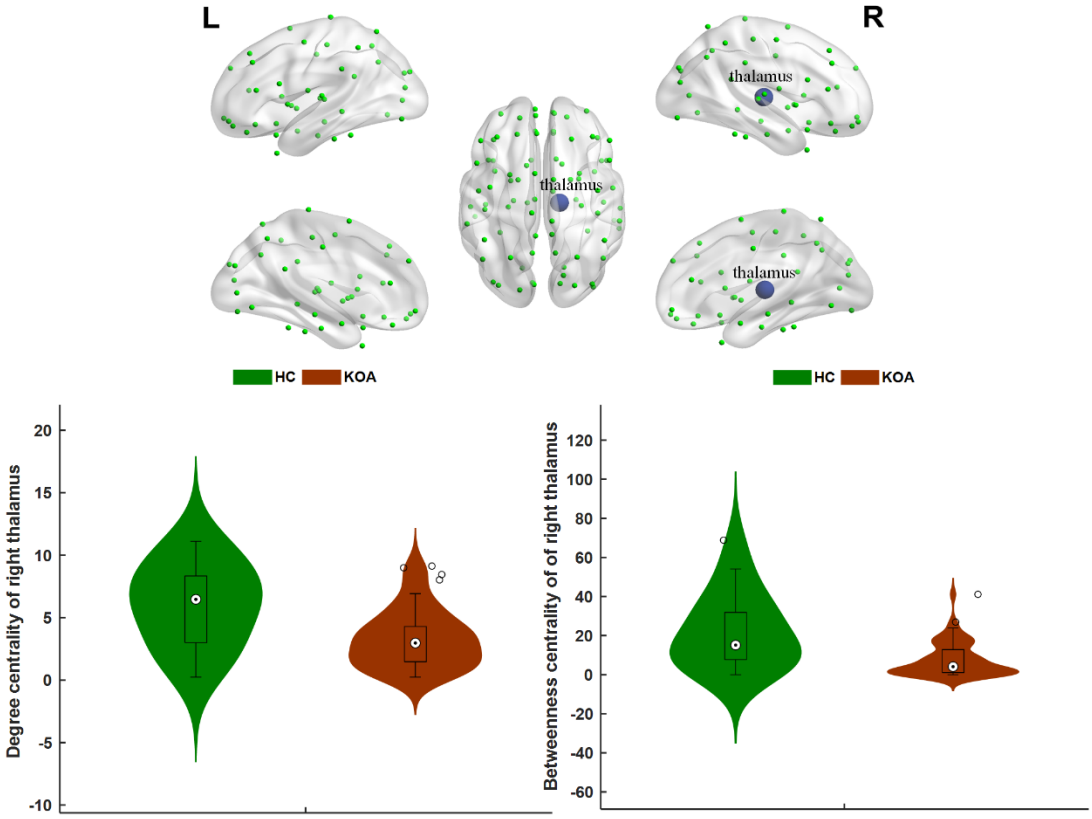

Figure 2. Group differences in degree centrality and betweenness centrality at the nodal level. Insignificant nodes are shown as green spheres, whereas blue (KOA< HC) spheres denote significant differences after FDR correction. Violin plots illustrating the area under the curve (AUC) parameters of degree centrality and betweenness centrality of the right thalamus for KOA patients and HCs.

3.2. Group comparisons of functional connectivity within and between RSNs

Nine functionally classical RSNs were extracted via visual inspection from all subjects (**Figure 3**). Compared with HCs, patients with KOA showed increased FC in left medial frontal gyrus of the anterior default mode network (aDMN), decreased FC in right insula of the salience network (SN), and reduced right superior tempror gyrus of the auditory network (AUN) compared with HCs (**Figure 4** and **Table 1**). No significant differences were observed in inter-network FC between KOA patients and HCs.

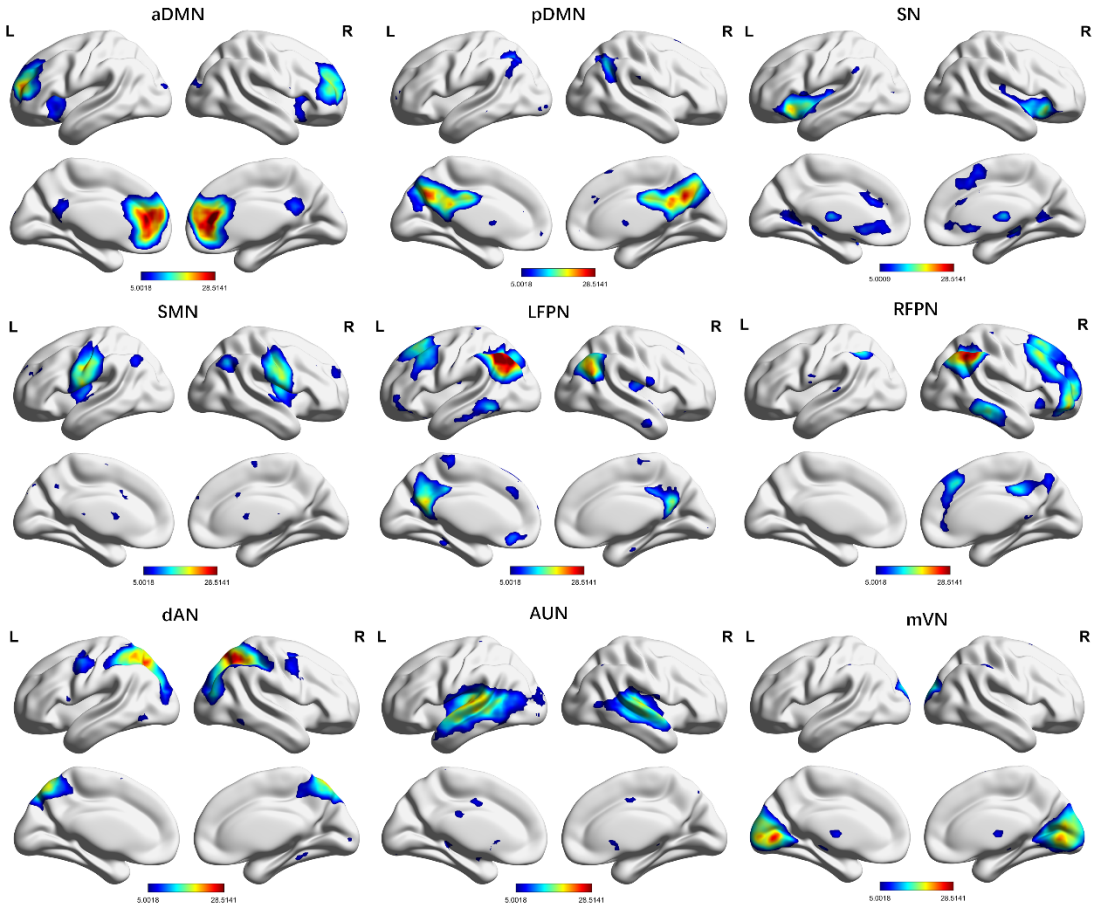

Figure 3. Spatial maps of one-sample t-test in nine RSNs of all subjects. The colorbar indicates the *t* value. aDMN: anterior default mode network; pDMN: posterior default mode network; SN: salience network, SMN: sensorimotor network; LFPN: left frontoparietal network; RFPN: right frontoparietal network; dAN: dorsal attention network; AUN: auditory network; mVN: medial visual network.

Table 1. Brain regions with significant differences in intra-network functional connectivity between KOA patients and healthy controls

RSN	Brain Regions	Cluster Size	MNI			Peak t Score
			X	Y	Z	
aDMN	L Medial frontal gyrus	43	-18	33	21	5.11
SN	R Insula	66	42	21	-9	-4.78
AUN	R Superior tempror gyrus	17	33	0	-18	-5.38

aDMN: anterior default mode network; SN: salience network; AUN: auditory network; MNI, Montreal Neurologic Institute; L, left; R, right.

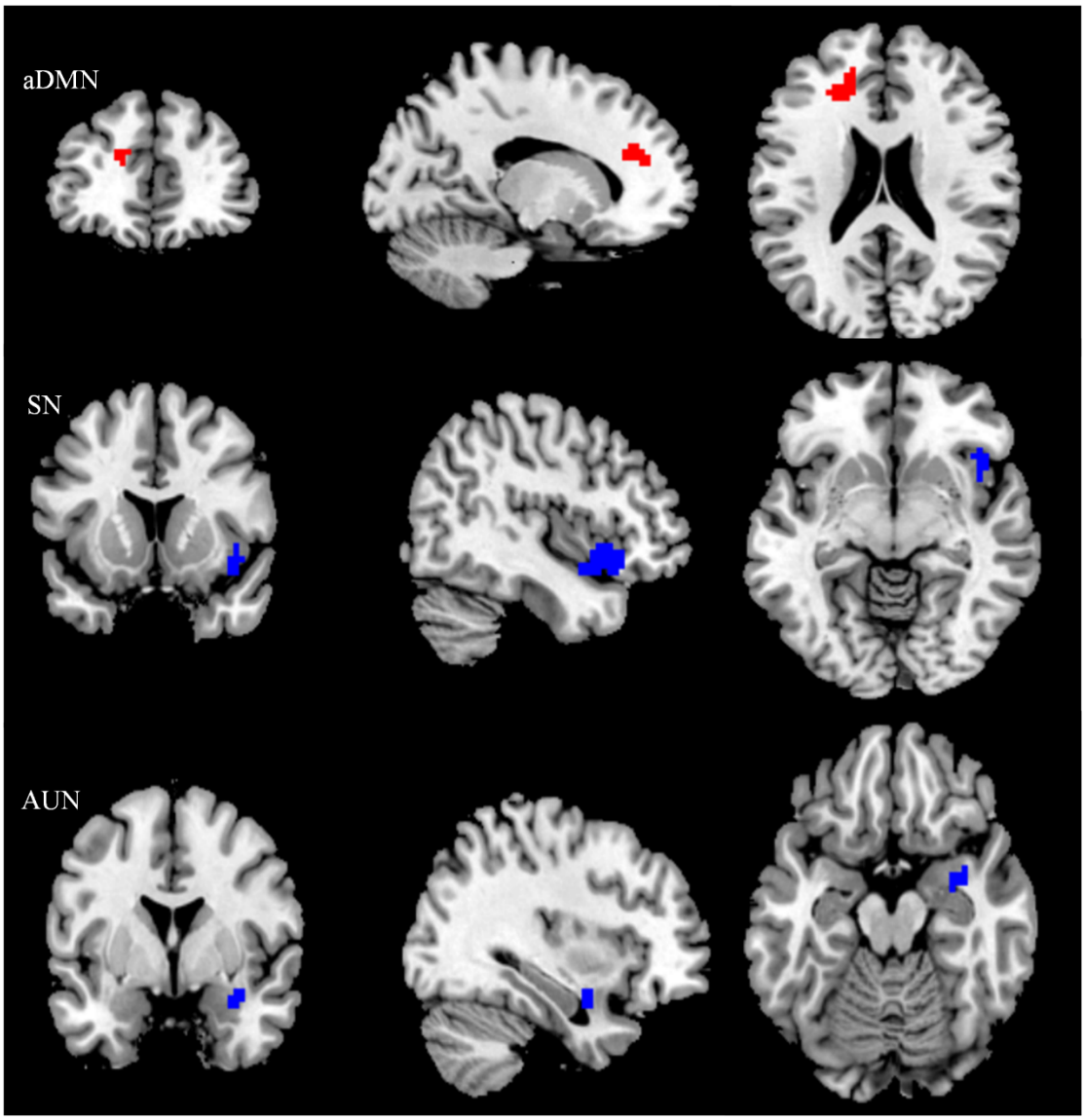

Figure 4. Comparison of intra-network functional connectivity between the KOA and HC groups. The red volume indicates a region whose functional connectivity was increased in KOA compared with HCs. Each blue volume indicates a region whose functional connectivity was decreased in the KOA .

4. Discussion

The study questioned whether differences existed in whole-brain network topology and how information transfer within intra- and inter-networks under chronic knee pain. Therefore, the study undertook unsupervised graph-theory-based analyses and ICA to identify a widespread network-level pathophysiological profile in KOA. Our key findings were as follows:

(1) Both groups displayed a small-world structure. Patients with KOA exhibited a decreased AUC of global efficiency and an increased AUC of assortativity at the global level. Additionally, decreased degree centrality and betweenness centrality in the right thalamus were observed in patients with KOA at the local level.

(2) Connectivity within the aDMN, SN, and AUN altered between the two groups.

4.1. Global and regional topological alterations of functional networks in KOA compared with HCs

At the global level, small-worldness, a fundamental trait of complex network structures [41,46], signifies an optimal equilibrium between global integration and local segregation. Both groups exhibited the characteristic small-world property, which aligns with findings reported in previous research studies [47,48]. Compared to controls, global efficiency was significantly decreased in the KOA group. Global efficiency is a robust indicator of information transmission within a network [43] and is commonly used to estimate the integration of brain networks. In this study, the observed decrease in global efficiency among KOA patients compared to controls may indicate impaired integration of information between key brain hubs. Such disrupted connectivity across distributed neural regions could contribute to altered cognitive and perceptual processing [49]. Abnormal topological organization has been reported in a previous study involving KOA cohorts [48]. However, global efficiency showed no significant difference between KOA patients and HCs, which is inconsistent with our findings. By contrast, KOA patients showed a higher value for assortativity. Assortativity, which measures network segregation, indicates neural networks' susceptibility to detrimental matters or neuropathological conditions [50,51]. A higher assortative value indicates that vertices are more likely to connect with other vertices of similar degree, leading to a more resilient network that can better inhibit the spread of information. Notably, the assortativity metric has been scarcely reported previously and may provide a more thorough assessment of the topological brain network architecture in KOA patients. Taken together, the decreased AUC of global efficiency and the increased AUC of assortativity indicate disruptions in brain networks related to functional integration and segregation in KOA patients. This suggests an imbalance between global integration and local segregation, highlighting disrupted energy expenditure in spontaneous brain activity and implying impaired parallel information transfer within the brain functional networks of these patients.

At the local level, the study found decreased nodal centrality in the right thalamus. Degree centrality measures the sum of links' weights connected to a node, depicting the significance of individual brain regions in influencing adjacent regions. Meanwhile, betweenness centrality evaluates how frequently a node participates in the shortest paths between all possible node pairs, reflecting its importance in facilitating communication within the network. Both metrics have been extensively used to assess brain network dysfunction across various clinical conditions [38,52,53]. Interestingly, the changes in nodal network topology observed in our study were primarily evident in centrality properties, particularly in the degree centrality and betweenness centrality of the right thalamus. The thalamus serves as a vital element of the pain matrix and its role in modulating nociception in neuropathic pain conditions has been extensively studied [54,57]. A seed-based analysis revealed abnormal resting-state and task-related functional connectivity and effective connectivity between the thalamus and cortex, with multiple regions involved, in the KOA cohort compared with HCs [58]. Our results extends these previous studies by revealing abnormal degree centrality and betweenness centrality of the right thalamus, further highlighting the thalamus's significant and intricate role in KOA.

4.2. Intra-network connectivity alterations in KOA compared with HCs

Our study provides evidence that KOA patients showed impaired intra-network FC of the aDMN, SN and AUN compared to HCs. The default mode network (DMN) is related to higher-order functions and internal states monitoring for the detection of prominent events. Many neuroimaging studies have shown that the DMN could regulate the perception of pain through autonomic and antinociceptive descending modulation networks [59,60].

Previous studies have consistently reported aberrant FC within the DMN in chronic pain conditions [8,61–65]. In our study, the medial frontal gyrus, a key component of the aDMN, exhibited reduced FC in KOA patients, highlighting its potential role in the functional reorganization of brain networks in KOA. The medial frontal gyrus, a region involving multiple psychological domains, including cognitive control, pain, and emotion [66–68], has been previously identified in fMRI studies on pain [69] and depression [70]. An epidemiological study estimated that 52% of patients with chronic pain contend with mental health challenges [71]. including depression, experiencing a decline in quality of life. Thus, it is believed that impaired FC in the medial frontal gyrus may contribute to the development of mood and emotional instabilities such as depression in KOA. In addition, the medial frontal gyrus is essential for attentional processing in relation to pain, contributing to the integration and interpretation of sensory inputs [72]. Therefore, the observed reductions in FC within the medial frontal gyrus could be linked to impairments in attentional control and sensory information processing in KOA patients.

The SN, responsible for monitoring sensory input changes and coordinating brain activity to prompt behavioral responses, is anticipated to be pivotal in chronic pain. Network alterations in the SN are most commonly reported in chronic pain conditions [73–77]. As the primary causal output within the SN, the insula is recognized as a crucial brain region involved in pain-attention interactions and serves as a key hub in pain regulation pathways [78,79]. Numerous neuroimaging studies have demonstrated abnormal FC driven by the insular cortex in patients across various chronic pain conditions [13,80–83]. Prior research has demonstrated that individuals with KOA exhibit decreased gray matter volume in the bilateral insular cortex, alongside elevated fractional amplitude of low-frequency fluctuations (fALFF) in the left insula [84]. In our study, KOA patients exhibited significantly reduced FC in the insular cortex compared with pain-free controls, further pointing to the importance of insular cortex in the functional reorganization of brain networks associated with chronic KOA pain.

AUN is believed to be involved in memory processes, and the changes in AUN may be associated with the memory impairment in chronic pain patients. However, the specific role of the AUN in neuroimaging research on pain remains to be fully elucidated and warrants further investigation.

Several limitations constrain the interpretation of the results for consideration. Firstly, our study is limited by its cross-sectional design and cannot uncover causal relationships in the etiology and persistence of KOA. Longitudinal studies, including investigations into remission and recurrence patterns across the lifespan, are needed. Secondly, the graph theoretical approach provides insights into only one aspect of the complex neural mechanisms underlying chronic pain disorders. Future research should explore additional facets of network topology. Lastly, the study is constrained by a relatively small control group, therefore introducing some uncontrolled bias. Future studies should validate these findings by running a similar sample of patients.

5. Conclusion

In summary, the study found abnormal topological architecture in functional brain networks and aberrant FC in specific cognitive networks in KOA patients. Measuring whole-brain FC patterns in KOA patients may elucidate pain sensitization mechanisms, thereby perpetuating symptoms and contributing to KOA development. Overall, our findings may elucidate the pathophysiology of KOA and ultimately inform mechanism-based therapies for various chronic pain conditions.

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Disclosure statement

The authors declare no conflict of interest.

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