Systematic Review

A Multimodal Meta-Analysis of Structural and Functional Alterations in the Brain of Knee Osteoarthritis

Shirui Cheng, MD[1,2], Xiaohui Dong, MD[3], Peng Lai, MM[1,2], Xingyao Chen, MM[1], Jun Zhou, MM[1], Zhengjie Li, MD[1,2], and Xi Wu, MD[1]

From: [1]Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, China; [2]Acupuncture and Brain Research Center, Chengdu University of Traditional Chinese Medicine, Chengdu, China; [3]School of Nursing, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Address Correspondence:
Xi Wu, MD
Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine
Chengdu, China;
E-mail: wuxii@cdutcm.edu.cn

Disclaimer: Shirui Cheng and Xiaohui Dong contributed equally to this article. This study is financially supported by the Sichuan Science and Technology Program (No.2022NSFSC0856), China Postdoctoral Science Foundation (No.2021MD703796), National Natural Science Foundation of China (No.82205288), Medical Technology Project of Health Commission of Sichuan Province (No.21PJ110). The funders did not play any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 07-24-2023
Revised manuscript received: 07-29-2023
Accepted for publication: 10-11-2023

Free full manuscript:
www.painphysicianjournal.com

Background: Abnormalities of structural and functional brain regions might influence the persistence of knee pain, the progression, and the response to treatments in knee osteoarthritis (KOA). These complex alterations present a challenge to the understanding of its mechanism.

Objectives: To meta-analyze the concurrence across structural and functional magnetic resonance imaging studies.

Study Design: Systematic review and meta-analysis.

Setting: This meta-analysis examined all voxel-based morphometric (VBM) and amplitude of low-frequency fluctuation (ALFF) studies involving the whole-brain alterations of KOA.

Methods: VBM and ALFF studies published up to May 7, 2023, were searched in the Web of Science, PubMed, EMBASE, Cochrane Library (CENTRAL), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database, Chongqing VIP, Wanfang Database. Two independent researchers carried out study screening, quality assessment, clinical data extraction, and neuroimaging data extraction. The whole-brain voxel-based gray matter (GM) and brain activity data of KOA were collected from eligible studies and meta-analyzed using the anisotropic effect size-signed differential mapping (AES-SDM).

Results: Fourteen studies were included in this study. In VBM meta-analyses, a total of 481 patients were enrolled in this study (252 KOA and 229 healthy patients). In the ALFF meta-analysis, a total of 518 patients were enrolled in this study (265 KOA and 253 healthy patients). According to the meta-analysis, KOA had increased GM volume in the right inferior frontal gyrus and decreased GM volume in the bilateral superior frontal gyrus, as well as increased brain activity in the left inferior frontal gyrus and inferior temporal gyrus, and decreased brain activity in the left middle occipital gyrus, right supramarginal gyrus, right superior frontal gyrus, and right superior parietal gyrus compared with healthy patients.

Limitations: Most of the ALFF studies included in this meta-analysis were conducted in China. Our findings are exclusively addressed by the VBM and ALFF studies. The meta-regression between the duration of KOA, pain intensity and abnormal gray matter, and functional activity of brain regions in patients with KOA were unable to be analyzed.

Conclusion: The results of this meta-analysis indicate that patients with KOA present significant abnormalities in GM volume and functional activity. These findings contribute to a better understanding of the structural and functional abnormalities seen in patients with KOA.

Key words: Knee osteoarthritis, meta-analysis, signed differential mapping, voxel-based morphometry, amplitude of low frequency fluctuation

Pain Physician 2024: 27:E557-E566

In many countries, chronic pain is proven to be related to neural sensitization, with the maturity and popularity of magnetic resonance technology in the past decades. Patients diagnosed with knee osteoarthritis (KOA) frequently experience persistent and intense rest-related pain (1), leading to reduced activity levels, significant changes in gray matter plasticity, impaired cognitive function, and an increased risk of developing dementia (2). Such discoveries concerning the abnormalities present in different structural and functional brain areas can hold significant implications for all recurring pain afflictions, including KOA, which is ranked among the most prevalent chronic illnesses.

Patients with KOA displayed measurable reductions in gray matter volumes in several key areas, particularly the left middle temporal gyrus, inferior temporal gyrus (3), precentral cortex (4), both bilateral orbital frontal cortex, right lateral prefrontal and postcentral cortices (5), together with bilateral amygdala, nucleus accumbent, and the primary somatosensory cortex on the ipsilateral side (6) compared with healthy individuals. Additionally, KOA patients presented decreased brain activity in various regions like the bilateral angular gyrus, precuneus gyrus, medial superior frontal gyrus, and left middle cingulate cortex (7,8), while also exhibiting elevated functional activity in certain parts, such as the bilateral amygdala and cerebellum posterior lobe (7). Despite these observed findings, there are significant variations across different studies pertaining to the exact locations where abnormal gray matter and functional activity appear.

To identify the most notable and consistently observed areas of abnormal gray matter and functional activity related to KOA, we conducted a meta-analysis that consolidated all existing whole-brain VBM and ALFF studies on the patient to data, using the anisotropic effect size signed differential mapping (AES-SDM) method (9,10). Utilizing this approach, we appraised both the VBM and ALFF meta-analyses' strength, as well as gauged the impact of age on these altered brain regions.

Methods

Search Strategies

A comprehensive search strategy to identify relevant neurological imaging studies on structural and functional changes related to KOA was conducted. Researchers Cheng and Dong independently performed a 2-state literature search using 8 databases, including Web of Science, PubMed, EMBASE, Cochrane Library (CENTRAL), Chinese Nation Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database, Chongqing VIP, and Wanfang Database. The search was carried out until May 7, 2023, with no restriction on publication data. During the English search, we used the following terms: (knee osteoarthritis OR knee pain) AND (magnetic resonance imaging OR MRI OR fMRI OR voxel-based morphometry OR VBM OR gray matter OR amplitude of low frequency fluctuation OR ALFF) AND resting state. This search strategy was tailored to suit the Chinese electronic databases. In cases where data were not available, or information was unclear, corresponding authors were contacted by e-mail for further clarification.

Selection Criteria

Studies that met the following criteria were included: (1) original articles published in English or Chinese academic journals; (2) patients recruited comprised of both KOA patients and healthy patients (HP); (3) the study examined structural or functional differences in the whole brain between KOA and HP; (4) results were reported using Montreal Neurological Institute (MNI) or Talairach coordinates; and (5) MRI scanners used had a magnet strength greater than or equal to 1.5T.

The criteria for exclusion were as follows: (1) studies that reported region of interest (ROI) findings or applied small volume corrections in pre-selected ROIs; or (2) datasets that were already covered by one or more articles; or (3) patients with concomitant, non-negligible medical conditions; or (4) patients who were adolescents. Additionally, when the same or similar datasets were used in multiple studies, we included only data from the analysis using the largest sample size.

Recorded Variables

The following information from the studies that met our inclusion criteria was extracted: first author, year of publication, sample size, mean age of patients, MRI scanner (1.5T or 3.0T), full width at half maximum (FWHM), and statistical threshold. We also identified statistically significant coordinates that included the direction of gray matter volume or density, or differential activity between KOA patients and HP. The relevant information has been compiled into Table 1 and 2.

Quality Assessment

The quality of all included studies was evaluated

Table 1. *Demographic and clinical characteristics of patients in VBM studies included in the meta-analysis.*

Study	Number		Mean Age (year)		MRI scanner	Smooth (FWHM)	Statistical threshold	Quality score
	KOA	HP	KOA	HP				
Baliki et al 2011	20	46	53.05	38.77	3.0T	8	TFCE corrected	11.5
Wu et al 2012	16	20	48.50	49.70	3.0T	6	Alphasim corrected	11
Zhang et al 2014	32	20	48.53	49.07	3.0T	NA	uncorrected	9.5
Wang et al 2017	45	15	60.64	NA	3.0T	8	uncorrected	11
Lewis et al 2018	29	18	71.00	68.00	3.0T	2	TFCE corrected	11.5
Liao et al 2018	30	30	56.50	55.20	3.0T	8	FWE corrected	12
Guo et al 2021	13	13	55.50	53.90	3.0T	10	Alphasim corrected	11.5
Kang et al 2022	37	37	71.60	69.50	1.5T	8	Alphasim corrected	11
Ma et al 2023	30	30	57.40	58.70	3.0T	6	uncorrected	10.5

Abbreviations: FWE, family-wise error; FWHM, full width at half maximum; HP, healthy patients; KOA, knee osteoarthritis; MRI, magnetic resonance imaging; NA, not available; T, tesla; TFCE, threshold-free cluster enhancement; VBM, voxel-based morphometry.

Table 2. *Demographic and clinical characteristics of patients in ALFF studies included in the meta-analysis.*

Study	Number		Mean Age (year)		MRI scanner	Smooth (FWHM)	Statistical threshold	Quality score
	KOA	HP	KOA	HP				
Wu et al 2012	16	20	48.50	49.70	3.0T	6	Alphasim corrected	11
Zhang et al 2014	32	20	48.53	49.07	3.0T	NA	uncorrected	9.5
Tang et al 2019	50	50	52.32	54.92	3.0T	NA	FWE corrected	10.5
Wang et al 2019	18	14	65.40	64.90	3.0T	NA	GRF corrected	11
Lan et al 2020	23	23	71.20	70.80	3.0T	6	GRF corrected	11.5
Qu et al 2021	13	13	55.50	53.90	3.0T	4	Alphasim corrected	10
Cai et al 2022	80	80	52.35	53.01	3.0T	NA	uncorrected	11
Ma et al 2023	16	16	61.13	61.13	3.0T	8	FDR corrected	10.5

Abbreviations: ALFF, amplitude of low frequency fluctuation; FDR, false discovery rate; FWE, family-wise error; FWHM, full width at half maximum; GRF, gaussian random field; HP, healthy patients; KOA, knee osteoarthritis; MRI, magnetic resonance imaging; NA, not available; T, tesla.

using a 12-point checklist, which was adapted from those used in previous meta-analyses. The checklist examined various aspects, including the demographic characteristics of the patients and critical scanner parameters, as well as methodological details (Table S1).

Data Extraction

Two investigators (Lai and Chen) conducted study selection and data extraction independently using a standardized approach, with any discrepancies being resolved by a third investigator (Zhou). This meta-analysis strictly followed the guidelines set forth in the Preferred Reporting Items for Meta-Analysis (PRISMA).

Meta-Analyses of Structural and Functional Abnormalities

A whole-brain voxel-wise meta-analysis using AES-SDM (https://www.sdmproject.com/software) (10,11) was conducted to examine changes in brain structure and activity. Firstly, retrieved peak information was integrated using a Gaussian kernel to rebuild the effect size and variance maps, with larger effect sizes assigned to voxels closer to the peaks. To avoid false-positive results, the full width at half maximum (FWHM) was fixed at 20 mm (10). Voxel-wise study maps were generated by taking into account sample size, intra-study variability, and between-study heterogeneity to determine random-effects means. The meta-analysis means were then applied with thresholds set to default parameters (voxel threshold $P < 0.005$, peak height threshold $z > 1.00$, and cluster size threshold > 10 voxels) (10). Statistical assessment of the meta-analysis effect-size map was carried out by comparing it to a null distribution created using a permutation algorithm. We also performed a leave-one-out jackknife sensitivity analysis to assess the reproducibility of VBM and ALFF findings after methodically removing each study. To investigate any influence from small or few studies, funnel plots of

the peaks of the main findings were conducted. Lastly, we conducted the Egger test to check for publication bias (12).

Meta-Regression Analysis

To assess the potential impacts of patient characteristics such as age of KOA on changes in the brain, a meta-regression analysis was conducted using a weighted approach based on sample size and intra- and between-study variances (10). To minimize false associations, we decreased the probability threshold to 0.005. Only results for the slope and one extreme of the regressor were included, while regions that were not detected in the main analysis were excluded.

Results

General Information of the Included Studies

Our search strategy yielded 857 articles, and after screening, 14 were deemed suitable for inclusion in this meta-analysis (Fig. 1) (3,5-8,13-21). Among these, 3 studies employed both VBM and ALFF methods to explore structural and functional variations between KOA and HP (16-18). These studies were regarded as 2 separate contributions in the meta-analysis. Therefore, the total number of studies included in our analysis was increased to 17. Out of the studies included, 9 reported changes in gray matter volume (either increase or decrease) in patients with KOA (3,5,6,13-18), while 8 reported differences in brain activity (7,8,16-21). The VBM meta-analyses involved a total of 481 patients, consisting of 252 individuals with KOA (mean age: 57.53 years) and 229 HP (mean age: 54.81 years). Similarly, the ALFF meta-analysis comprised a total of 518 patients, including 265 KOA patients (mean age: 55.27 years) and 253 HP (mean age: 56.28 years). There was no statistically significant age difference found between individuals with KOA and HP ($P > 0.05$). The studies had mean quality scores of 11.06 and 10.63, respectively, out of a possible total score of 12, indicating a high-quality of research. Fig. 1 presents details of the literature search and criteria used for article inclusion. Tables 1 and 2 provide information about the clinical variables and technical details of the included studies.

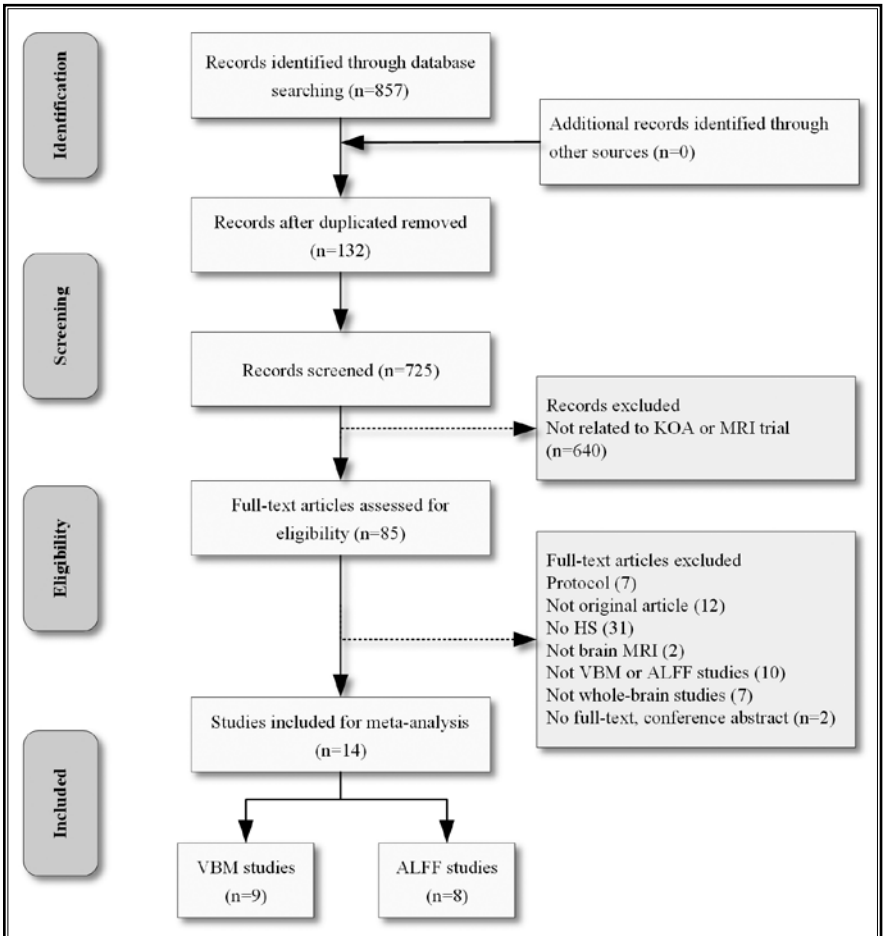

Fig. 1. *The flow diagram for VBM and ALFF studies is included in the present meta-analysis. Abbreviations: ALFF, amplitude of low-frequency fluctuation; HP, healthy patients; KOA, knee osteoarthritis; MRI, magnetic resonance imaging; VBM, voxel-based morphometry.*

Meta-Analyses of Gray Matter Changes

The AES-SDM analysis revealed that patients with KOA demonstrated increased GM volume in the right inferior frontal gyrus (P = 0.000, z = 1.043) alongside reduced GM volume in the right superior frontal gyrus (P = 0.000, z =

-2.015), left superior frontal gyrus (*P* = 0.001, z = -1.739), left middle temporal gyrus (*P* = 0.000, z = -1.990) compared with HP (Table 3, Fig. 2).

Meta-Analyses of ALFF Abnormalities

The AES-SDM findings revealed that patients with KOA displayed increased brain activity in the

Table 3. *GM differences between KOA patients and healthy patients.*

	MNI coordinates			SDM z-score [a]	*P*-value [b]	Number of voxels [c]	Cluster breakdown (number of voxels)	heterogeneity	Sensitivity
	x	y	z						
KOA > HP									
R inferior frontal gyrus	58	20	24	1.043	0.000	287	R inferior frontal gyrus, triangular part, BA44, BA45, BA48 (150)	Yes	8/9
							R inferior frontal gyrus, opercular part, BA44, BA48 (132)		
KOA < HP									
R superior frontal gyrus	12	54	34	-2.015	0.000	731	R superior frontal gyrus, BA9, BA10 (731)	No	9/9
							R middle frontal gyrus, BA46 (63)		
L superior frontal gyrus	0	54	26	-1.739	0.001		L superior frontal gyrus, BA9, BA10 (209)	No	6/9
L middle temporal gyrus	-58	-14	-14	-1.990	0.000	815	L middle temporal gyrus, BA20, BA21, BA22 (497)	No	7/9
							L superior temporal gyrus, BA21, BA22, BA48 (88)		
							L inferior temporal gyrus, BA20 (64)		
							L temporal pole, BA21 (12)		

[a]Peak height threshold: z > 1. [b]Voxel probability threshold: *P* < 0.005. [c]Cluster extent threshold: regions with less than 10 voxels are not reported in the cluster breakdown. Abbreviations: BA, Brodmann area; GM, gray matter; HP, healthy patients; KOA, knee osteoarthritis; L, left; MNI, Montreal Neurological Institute; R, right; SDM, signed differential mapping; VBM, voxel-based morphometry.

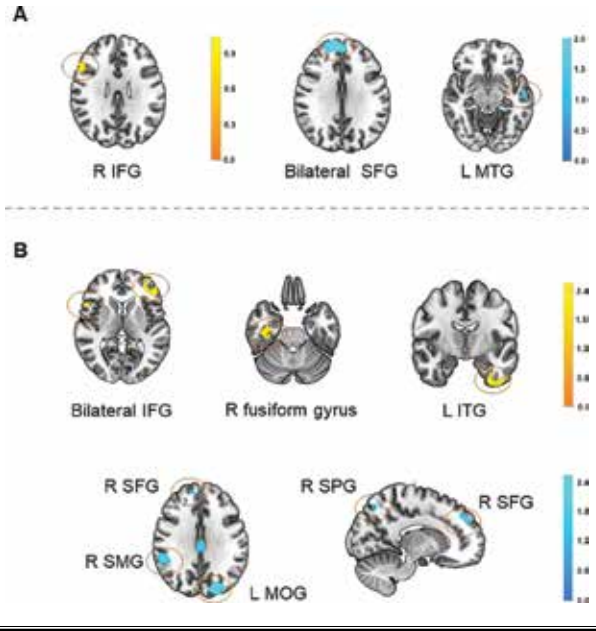

Fig. 2. *A) Gray matter volume alterations of brain regions in KOA patients compared with healthy patients. B) Functional activity alterations of brain regions in KOA patients compared with healthy patients.*
Abbreviations: IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; L, left; MOG, middle occipital gyrus; MTG, middle temporal gyrus; R, right; SFG, superior frontal gyrus; SMG, supramarginal gyrus; SPG, superior parietal gyrus

left inferior frontal gyrus (P = 0.000, z = 2.632), left inferior temporal gyrus (P = 0.000, z = 2.617), right fusiform gyrus (P = 0.000, z = 2.598), and right inferior frontal gyrus (P = 0.000, z = 2.615), while manifesting decreased brain activity in the left middle occipital gyrus (P = 0.000, z = -2.643), right supramarginal gyrus (P = 0.001, z = -1.974), right superior frontal gyrus (P = 0.001, z = -1.940), right superior parietal gyrus (P = 0.004, z = -1.535) compared to HP (Table 4, Fig. 2).

Meta-Regression

A meta-regression analysis was performed to investigate the potential impact of age on structural and functional brain regions in KOA patients. The results demonstrated that the mean age of KOA patients had an impact on gray matter volume alterations in the left middle temporal gyrus (P = 0.000, z = -2.345) in VBM studies (Table 5). Moreover, the age of KOA patients was associated with changes in brain activity in the right superior frontal gyrus (P = 0.001, z = -2.813) in ALFF studies (Table 5).

Table 4. *Brain activity differences between KOA patients and healthy patients.*

	MNI coordinates			SDM z-score [a]	P-value [b]	Number of voxels [c]	Cluster breakdown (number of voxels)	heterogeneity	Sensitivity
	x	y	z						
KOA > HP									
L inferior frontal gyrus	-46	38	6	2.632	0.000	854	L inferior frontal gyrus, BA45, BA46 (291) L middle frontal gyrus, BA10, BA45, BA46, BA47 (410)	No	7/8
L inferior temporal gyrus	-34	-4	-44	2.617	0.000	472	L inferior temporal gyrus, BA20, BA36 (171) L fusiform gyrus, BA20 (72)	No	6/8
R fusiform gyrus	38	-14	-30	2.598	0.000	265	R fusiform gyrus, BA20 (160) R parahippocampal gyrus, BA20 (28) R inferior temporal gyrus, BA20 (20)	No	7/8
R inferior frontal gyrus	52	22	16	2.615	0.000	255	R inferior frontal gyrus, BA44, BA45, BA48 (224)	No	7/8
KOA < HP									
L middle occipital gyrus	-26	-78	36	-2.643	0.000	848	L middle occipital gyrus, BA7, BA19 (395) L precuneus, BA7 (126) L superior occipital gyrus, BA18 (83) L cuneus cortex, BA19 (47) L superior parietal gyrus, BA19 (28)	No	7/8
R supramarginal gyrus	54	-44	28	-1.974	0.001	391	R supramarginal gyrus, BA40, BA48 (199) R superior temporal gyrus, BA42, BA48 (49) R angular gyrus, BA48 (10)	No	5/8
R superior frontal gyrus	18	46	38	-1.940	0.001	309	R superior frontal gyrus, BA9 (154) R middle frontal gyrus, BA9 (78)	No	8/8
R superior parietal gyrus	12	-68	52	-1.535	0.004	35	R superior parietal gyrus, BA7 (15) R precuneus, BA7 (15)	No	3/8

[a]Peak height threshold: z > 1. [b]Voxel probability threshold: P < 0.005. [c]Cluster extent threshold: regions with less than 10 voxels are not reported in the cluster breakdown. Abbreviations: BA, Brodmann area; GM, gray matter; HP, healthy patients; KOA, knee osteoarthritis; L, left; MNI, Montreal Neurological Institute; R, right; SDM, signed differential mapping.

Table 5. *Meta-regression analysis for correlation between GM and ALFF abnormalities and age of KOA patients.*

Region	MNI coordinate			SDM z-score [a]	*P*-value [b]	number of voxels [c]
	x	y	z			
GM abnormalities						
L middle temporal gyrus	-62	-28	-4	-2.345	0.000	696
ALFF abnormalities						
R superior frontal gyrus	14	56	26	-2.813	0.001	88

[a]Peak height threshold: z > 1. [b]Voxel probability threshold: $P < 0.005$. [c]Cluster extent threshold: Regions with less than 10 voxels are not reported in the cluster breakdown. Abbreviations: ALFF, amplitude of low frequency fluctuation; GM, gray matter; KOA, knee osteoarthritis; L, left; MNI, Montreal Neurological Institute; R, right; SDM, signed differential mapping.

Heterogeneity Analysis, Sensitivity Analysis and Publication Bias

After conducting VBM meta-analysis and heterogeneity analysis, significant heterogeneity was discovered in the right inferior frontal gyrus ($P < 0.005$). Based on the leave-one-out jackknife sensitivity analysis, the right superior frontal gyrus remained intact in 9 combinations which can be found in Table S2. As illustrated in Fig. S1, the funnel plots suggested that the principal findings were driven by a minimum of 8 VBM studies. Further analysis of publication bias revealed that Egger test yielded insignificant results for the peaks of the altered brain regions in the VBM meta-analysis ($P = 0.613$).

During ALFF studies, the heterogeneity analysis showed that no significant heterogeneity was found among the observed brain activity abnormalities ($P > 0.005$). Based on the leave-one-out jackknife sensitivity analysis, the right superior frontal gyrus was found to be unaffected in 8 combinations, which can be located in Table S3. Furthermore, as shown in Fig. S2, the funnel plots illustrated that the primary findings were driven by a minimum of 6 ALFF studies. Analysis of publication bias revealed that Egger test produced insignificant results for the peaks of the altered brain regions in the ALFF meta-analysis ($P = 0.002$).

Discussion

To our knowledge, this is the first meta-analysis of VBM and ALFF studies utilizing image-based techniques to investigate differences between patients with KOA and HP. The primary findings indicated that those who had KOA exhibited significantly increased GM volume in the right inferior frontal gyrus and decreased GM volume in bilateral superior frontal gyrus compared to HP. Additionally, there was an increase in brain activity observed in the left inferior frontal gyrus and inferior temporal gyrus, as well as a decrease in the activity of the left middle occipital gyrus, right supramarginal gyrus, right superior frontal gyrus, and right superior parietal gyrus. According to the 14 studies reviewed, the most reliable findings involved gray matter reduction and decreased functional activity in the right superior frontal gyrus. The meta-regression analysis also demonstrated that age was associated with abnormal gray matter in the left middle temporal gyrus and altered functional activity in the right superior frontal gyrus.

Pain is a multidimensional experience that encompasses various aspects, including sensory recognition, emotional motivation, and cognitive evaluation (22). The superior frontal gyrus, which is involved in numerous processes like cognitive functional and emotional processing (23), showed a decrease in both GM volume and functional activity in patients with KOA, supporting previous findings from behavioral and functional MRI studies (7,24). Additionally, patients with KOA exhibited an increase in both GM volume and functional activity in the bilateral inferior frontal gyrus, a region associated with pain processing (25,26). These findings align well with other functional MRI studies that have reported abnormal responses in the frontal cortex of patients with KOA and other chronic pain disorders (22,27,28). The prefrontal cortex is a critical region for top-down pain regulation and cognitive control of emotion-driven behaviors (28,29). There was a significant increase in prefrontal cortex activity in patients with KOA, which plays a role in the suppression of chronic pain (30). High brain processing activity transforms sensory stimuli into perceptual signals, and these signals are utilized to regulate the flow of incoming sensory stimuli at the entry point to the central nervous system, known as the dorsal horn (28). Research has demonstrated the involvement of the prefrontal cortex (PFC) in placebo analgesia and the connections between pain and depression, anxiety, and cognition decline. Notably, the loss of gray matter in the PFC is often reversible following successful treatment of chronic pain (28).

The middle temporal gyrus serves as the central structure of the default mode network (31). The temporal lobe is known to be associated with attentional orientation (32) and plays a significant role in pain perception in other chronic pain disorders (33). The inferior temporal gyrus is involved in memory, social cognition, action observation, and the integration of sensory information from multiple modalities. In stress disorders, a decrease in the volume of the inferior temporal cortex has been found to be inversely related to self-reported anxiety (34). Although the middle temporal gyrus and inferior temporal gyrus do not directly regulate pain, changes in their GM volume and functional activity may be associated with the comorbidities of KOA, such as cognitive and emotional impairments caused by chronic knee pain (24). Studies have shown that patients with KOA exhibit reduced resting-state functional connectivity between the left middle temporal and the right superior frontal gyrus, as well as the left medial superior frontal gyrus (24). It suggests that abnormal structure and function within these areas may contribute to impaired pain regulation, emotional disturbances, and ultimately increase the risk of persistent pain in patients with KOA.

The occipital cortex is responsible for visual perception and the integration of visual, auditory, and tactile information (35,36). Previous studies have shown structural and functional alterations in the occipital cortex in patients with chronic pain disorders (37,38), which are believed to be related to the integration of visual cues with motor pathways. This integration allows for the coordination of limb movements based on visual feedback, enabling effective interaction with the environment (39). Interestingly, similar structural and functional alterations have also been observed in patients with KOA (13,18,21), suggesting impaired visuospatial attention reallocation for self-regulation in these individuals. Additionally, patients with KOA exhibited decreased functional activity in the superior parietal gyrus, a region that is part of a network related to pain perception. Reduced functional connectivity between parietal regions and the sensorimotor system may indicate a more segregated and less efficient system (40), which can affect one's ability to adapt behavior in response to painful stimuli (41).

This study has a few limitations that should be considered. Firstly, the Egger test revealed a potential publication bias as the majority of the ALFF studies included in this meta-analysis were conducted in China. Because most of the eligible ALFF studies included in this meta-analysis were Chinese. Secondly, our findings are limited by the constraints of the VBM and ALFF methods, which may not capture other spatially complex and subtle group differences in brain metrics, such as regional homogeneity, cortical thickness, and white matter. Thirdly, due to a lack of available data, we were unable to directly analyze the correlations between the duration of KOA, pain intensity, emotion state, abnormal gray matter, and functional activity in specific brain regions of patients with KOA.

Conclusions

The results of this meta-analysis indicate that patients with KOA present significantly increased GM volume in the right inferior frontal gyrus, as well as decreased GM volume in the bilateral superior frontal gyrus. Furthermore, there is increased brain activity in the left inferior frontal gyrus and inferior temporal gyrus, along with decreased brain activity in the left middle occipital gyrus, right supramarginal gyrus, right superior frontal gyrus, right superior parietal gyrus. These findings contribute to a better understanding of the structural and functional abnormalities seen in patients with KOA. The meta-regression analyses provide additional insights into whether age is associated with these alterations in GM volume and functional activity in individuals with KOA. However, there is a need for larger prospective longitudinal studies that combine structural and functional MRI to further investigate the associations between these variables and GM volume and functional activity in the same study.

Data Availability Statement

The datasets analyzed in the current study are available from the corresponding author upon reasonable request.

Author Contributions

Study conception and design: Shirui Cheng and Xiaohui Dong. Analysis strategy, data acquisition, and analysis: Shirui Cheng, Xiaohui Dong, Peng Lai, Xingyao Chen, and Jun Zhou. Manuscript drafting: Shirui Cheng and Xiaohui Dong. Manuscript revision and publication approval: all authors.

References

1. Power JD, Perruccio AV, Gandhi R, et al. Neuropathic pain in end-stage hip and knee osteoarthritis: Differential associations with patient-reported pain at rest and pain on activity. *Osteoarthritis Cartilage* 2018; 26:363-369.
2. Huang SW, Wang WT, Chou LC, Liao CD, Liou TH, Lin HW. Osteoarthritis increases the risk of dementia: A nationwide cohort study in Taiwan. *SciRep* 2015; 5:10145.
3. Kang BX, Ma J, Shen J, et al. Altered brain activity in end-stage knee osteoarthritis revealed by resting-state functional magnetic resonance imaging. *Brain Behav* 2022; 12:e2479.
4. Barroso J, Vigotsky AD, Branco P, et al. Brain gray matter abnormalities in osteoarthritis pain: A cross-sectional evaluation. *Pain* 2020; 16:2167-2178.
5. Liao X, Mao C, Wang Y, et al. Brain gray matter alterations in Chinese patients with chronic knee osteoarthritis pain based on voxel-based morphometry. *Medicine (Baltimore)* 2018; 97:e0145.
6. Lewis GN, Parker RS, Sharma S, Rice DA, McNair PJ. Structural brain alterations before and after total knee arthroplasty: A longitudinal assessment. *Pain Med* 2018; 19:2166-2176.
7. Lan F, Lin G, Cao G, et al. Altered intrinsic brain activity and functional connectivity before and after knee arthroplasty in the elderly: A resting-state fMRI study. *Front Neurol* 2020; 11:556028.
8. Cai G, Chen R, Xu S, Tao J, Liu J. Characteristics of amplitude of low frequency fluctuation in patients with knee osteoarthritis and low back pain. *Chinese Journal of Rehabilitation Theory and Practice* 2022; 28:602-608.
9. Radua J, Rubia K, Canales-Rodríguez EJ, Pomarol-Clotet E, Fusar-Poli P, Mataix-Cols D. Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. *Front Psychiatry* 2014; 5:13.
10. Radua J, Mataix-Cols D, Phillips ML, et al. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *Eur Psychiatry* 2012; 27:605-611.
11. Radua J, Borgwardt S, Crescini A, et al. Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication. *Neurosci Biobehav Rev* 2012; 36:2325-2333.
12. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *Br J Psychiatry* 2009; 195:393-402.
13. Baliki MN, Schnitzer TJ, Bauer WR, Apkarian AV. Brain morphological signatures for chronic pain. *PloS One* 2011; 6:e26010.
14. Wang Z. Explore the neural mechanism of exercies rehabilitation of knee osteoarthritis. *Fujian University of Traditional Chinese Medicine*, 2017.
15. Guo H, Wang Y, Qiu L, et al. Structural and Functional Abnormalities in Knee Osteoarthritis Pain Revealed With Multimodal Magnetic Resonance Imaging. *Front Hum Neurosci* 2021; 15:783355.
16. Wu F. The research of chronic pain patient with resting state functional MRI and voxel based morphometry. *Chongqing Medical University*, 2012.
17. Zhang H, Wang J, Yao X. The research of chronic pain patient with resting state functional MRI and coxel based morphometry. *Journal of Gannan Medical University* 2014; 34.
18. Ma X, Zhang C, Zheng Y, et al. Multimodal magnetic resonance imaging study of brain structure and function changes in patients with knee osteoarthritis. *Journal of Molecular Imaging* 2023; 46:21-27.
19. Tang C. Mechanism of acupuncture influence on default mode network in knee osteoarthritis patients: A resting-state functional magnetic resonance imaging study. *Chengdu University of Traditional Chinese Medicine*, 2019.
20. Wang X, Wang K, Zhang X, Bao Z, Jiang Q, Zhang B. The correlation between altered brian fMRI and pain perception before and after operation in patients with knee osteoarthritis. International *Journal of Medical Radiology* 2019; 42:255-259,284.
21. Qu B, Wang H, Zhao C, et al. Clinical efficacy evaluation and central mechanism study of acupuncture in treating chronic knee osteoarthritis. *Journal of Xinjiang Medical University* 2021; 44.
22. Mercer Lindsay N, Chen C, Gilam G, Mackey S, Scherrer G. Brain circuits for pain and its treatment. *Sci Transl Med* 2021; 13:eabj7360.
23. Kraljević N, Schaare HL, Eickhoff SB, et al. Behavioral, anatomical and heritable convergence of affect and cognition in superior frontal cortex. *Neuroimage* 2021; 243:118561.
24. Kang BX, Ma J, Shen J, et al. Altered brain activity in end-stage knee osteoarthritis revealed by resting-state functional magnetic resonance imaging. *Brain Behav* 2022; 12:e2479.
25. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci* 2013; 14:502-511.
26. Liang M, Mouraux A, Hu L, Iannetti GD. Primary sensory cortices contain distinguishable spatial patterns of activity for each sense. *Nat Commun* 2013; 4:1979.
27. Che X, Cash RFH, Luo X, et al. High-frequency rTMS over the dorsolateral prefrontal cortex on chronic and provoked pain: A systematic review and meta-analysis. *Brain stimul* 2021; 14:1135-1146.
28. Ong WY, Stohler CS, Herr DR. Role of the prefrontal cortex in pain processing. *Mol Neurobiol* 2019; 56:1137-1166.
29. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: A literature review. *Arch Intern Med* 2003; 163:2433-2445.
30. Hiramatsu T, Nakanishi K, Yoshimura S, et al. The dorsolateral prefrontal network is involved in pain perception in knee osteoarthritis patients. *Neurosci Let* 2014; 581:109-114.
31. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 2008; 1124:1-38.
32. Hu G, Hu X, Yang K, et al. Restructuring of contralateral gray matter volume associated with cognition in patients with unilateral temporal lobe glioma before and after surgery. *Hum Brain Mapp* 2020; 41:1786-1796.
33. Schreiber KL, Loggia ML, Kim J, Cahalan CM, Napadow V, Edwards RR. Painful fter-sensations in fibromyalgia are linked to catastrophizing and differences in brain response in the medial temporal lobe. *J Pain* 2017; 18:855-867.
34. Kroes MC, Rugg MD, Whalley MG, Brewin CR. Structural brain abnormalities common to posttraumatic stress disorder and depression. *J Psychiatry Neurosci* 2011; 36:256-265.
35. Amedi A, Stern WM, Camprodon JA, et al. Shape conveyed by visual-to-auditory

sensory substitution activates the lateral occipital complex. *Nat Neurosci* 2007; 10:687-689.

36. Yu Q, Panichello MF, Cai Y, Postle BR, Buschman TJ. Delay-period activity in frontal, parietal, and occipital cortex tracks noise and biases in visual working memory. *PLoS Biol* 2020; 18:e3000854.
37. Yin T, Sun G, Tian Z, et al. The spontaneous activity pattern of the middle occipital gyrus predicts the clinical efficacy of acupuncture treatment for migraine without aura. *Front Neurol* 2020; 11:588207.
38. Li Z, Zhou J, Lan L, et al. Concurrent brain structural and functional alterations in patients with migraine without aura: an fMRI study. *J Headache Pain* 2020; 21:141.
39. Chen Y, Crawford JD. Allocentric representations for target memory and reaching in human cortex. *Ann Y Acad Sci* 2020; 1464:142-155.
40. Shine JM, Bissett PG, Bell PT, et al. The dynamics of functional brain networks: Integrated network states during cognitive task performance. *Neuron* 2016; 92(2):544-554.
41. Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci* 2011; 12:154-167.

Table S1. *Quality Assessment Checklist (1 point per criterion for fully satisfied, 0.5 for partially satisfied, 0 for otherwise).*

Category 1: Patients	Score (0/0.5/1)
1. Patients were evaluated prospectively, specific diagnostic criteria were applied, and demographic data were reported.	
2. Healthy patients were evaluated prospectively, and psychiatric and medical illnesses were excluded.	
3. Important variables (such as age, gender, illness duration, onset time, medication status, comorbidity, and severity of illness) were checked, either by stratification or statistically.	
4. Sample size per group > 10.	
Category 2: Methods for image acquisition and analysis	
5. Magnet strength ≥ 1.5T.	
6. MRI slice thickness ≤ 2 mm.	
7. The whole-brain analysis was automatically calculated with no prior regional selection.	
8. Coordinates were reported in a standard space.	
9. The imaging technique processing was described clearly enough to be reproducible.	
10. Measurements were described clearly enough to be reproducible.	
Category 3: Results and conclusions	
11. Statistical parameters were provided.	
12. Conclusions were consistent with the results obtained, and the limitations were discussed.	
TOTAL	/12

Abbreviations: MRI, magnetic resonance imaging; T, tesla.

Table S2. *Sensitivity analysis of VBM meta-analysis.*

Studies	Increased GM volume regions	Decreased GM volume regions			
	R inferior frontal gyrus	R superior frontal gyrus	L superior frontal gyrus	L middle temporal gyrus	R inferior frontal gyrus
Baliki et al 2011	yes	yes	yes	yes	yes
Wu et al 2012	yes	yes	no	yes	yes
Zhang et al 2014	yes	yes	no	yes	yes
Wang et al 2017	no	yes	no	yes	no
Lewis et al 2018	yes	yes	yes	yes	yes
Liao et al 2018	yes	yes	yes	yes	no
Guo et al 2021	yes	yes	yes	yes	no
Kang et al 2022	yes	yes	yes	no	yes
Ma et al 2023	yes	yes	yes	no	yes

Abbreviations: GM, gray matter; L, left; R, right; VBM, voxel-based morphometry.

Table S3. *Sensitivity analysis of ALFF meta-analysis.*

Studies	Increased ALFF regions				Decreased ALFF regions			
	L inferior frontal gyrus	L inferior temporal gyrus	R fusiform gyrus	R inferior frontal gyrus	L middle occipital gyrus	R supramarginal gyrus	R superior frontal gyrus	R superior parietal gyrus
Wu et al 2012	yes	yes	yes	yes	yes	no	yes	no
Zhang et al 2014	yes	yes	yes	yes	yes	no	yes	no
Tang et al 2019	yes	yes	yes	yes	yes	yes	yes	yes
Wang et al 2019	yes	yes	yes	yes	yes	yes	yes	no
Lan et al 2020	yes	no	yes	yes	yes	no	yes	no
Qu et al 2021	no	no	no	no	no	yes	yes	yes
Cai et al 2022	yes	yes	yes	yes	yes	yes	yes	yes
Ma et al 2023	yes	yes	yes	yes	yes	yes	yes	no

Abbreviations: ALFF, amplitude of low frequency fluctuation; L, left; R, right.

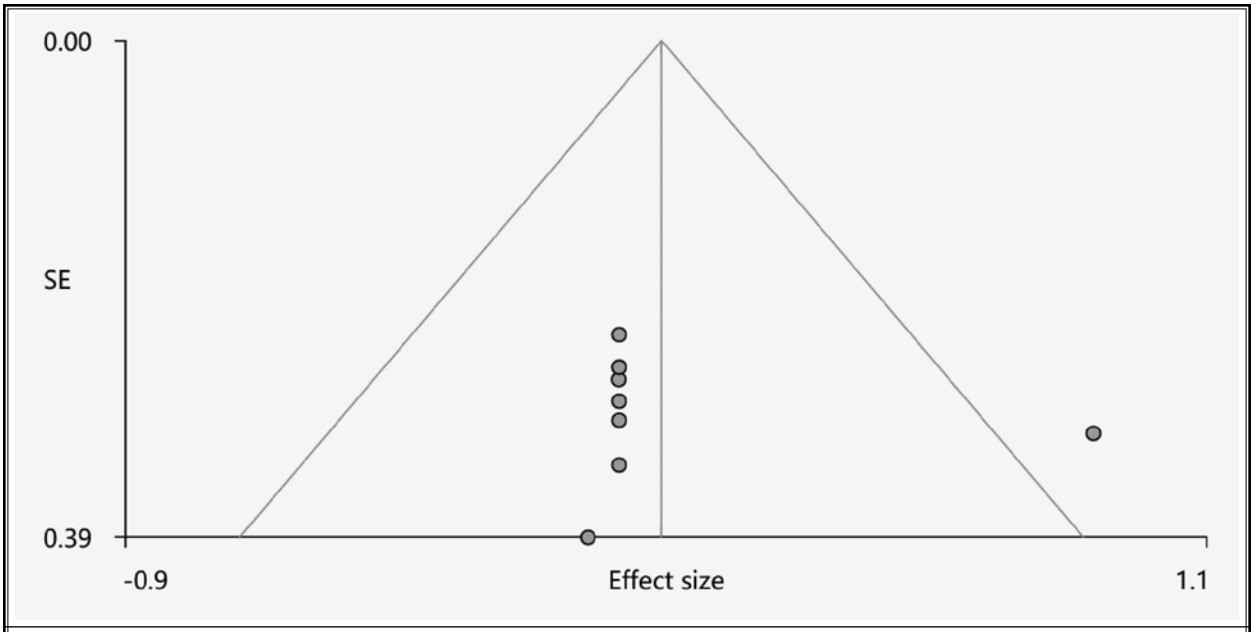

Fig. S1. *A funnel plots suggesting that the principal findings were driven by a minimum of 8 VBM studies.*

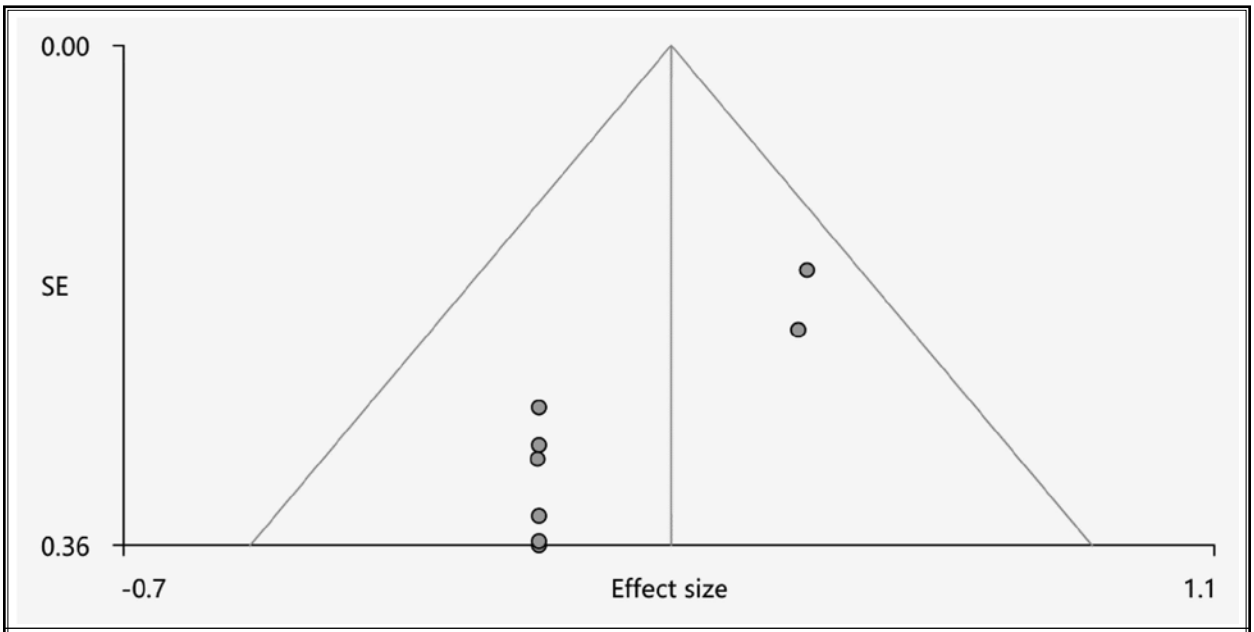

Fig. S2. *The funnel plots illustrated that the primary findings were driven by a minimum of 6 ALFF studies.*