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ORIGINAL RESEARCH

Mapping the Brain's Role in Osteoarthritis: New Evidence for Prevention

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Purpose: This study explores the causal link between brain structural parameters and Osteoarthritis (OA), aiming to prevent OA progression.

Patients and Methods: We used two-sample Mendelian randomization. In addition to European OA data with a sample size of 484,598, Firth correction OA data from the same source, and SPA correction OA data were included as outcome data. 3913 brain imaging-derived phenotypes (IDPs) from the UK Biobank were used as exposure data. Weighted median, MR Egger, and IVW validated causal correlations. Analyses of sensitivity and heterogeneity validated the robustness of the findings.

Results: Thirteen brain regions significantly linked to OA. Increased fractional anisotropy (FA) in the cingulate hippocampal gyrus (OR: 0.99, 95% CI: 0.98–1.00, P = 0.003), orientation diffusion(OD) in the fornix and Stria terminalis (OR: 0.99, 95% CI: 0.98–1.00, P = 0.004) and isotropic volume fraction (ISOVF) (OR: 0.99, 95% CI: 0.99–1.00, P = 0.039) in the fornix, as well as an increase in OD in the posterior thalamic radiation (R) (OR: 0.99, 95% CI: 0.98–1.00, P = 0.047) reduce OA risk as protective factors. Increased subparietal lobule area (OR: 0.99, 95% CI: 0.98–1.00, P = 0.045) and middle temporal gyrus volume (OR: 0.98, 95% CI: 0.97–1.00, P = 0.029) also demonstrated a protective effect against OA. Conversely, OA risk was increased by increases in the medial thalamic tract's OD (OR: 1.01, 95% CI: 1.00–1.02, P = 0.034), the cerebral peduncle's intracellular volume fraction (ICVF) (OR: 1.01, 95% CI: 1.00–1.01, P = 0.010), the anterior limb of the internal capsule's ISOVF (OR: 1.01, 95% CI: 1.00–1.01, P = 0.033), and the posterior thalamic radiation(L) 's MO (OR: 1.02, 95% CI: 1.00–1.03, P = 0.024). Interestingly, lateral orbitofrontal volume decreased (R: OR: 0.99, 95% CI: 0.98–1.00, P = 0.013; L: OR: 0.99, 95% CI: 0.98–1.00, P = 0.038), while medial orbitofrontal increased risk (OR: 1.02, 95% CI: 1.00–1.04, P = 0.024).

Conclusion: Our findings provide genetic evidence for the prevention of OA based on the bone-brain axis and suggest a clinical strategy for integrated pain-psychomotor intervention through neural nociceptive modulation, limbic circuit stabilization, and motor pathway enhancement.

Keywords: bone, brain, Mendelian randomization, osteoarthritis

Introduction

OA is a degenerative joint disease that can affect almost any joint. Damage to articular cartilage usually leads to cartilage degradation and ultimately osteoarthritis because of its limited ability to repair itself.[1] A study on the burden of disease in osteoarthritis, published in The Lancet, predicts that by 2050, nearly 1 billion people worldwide will have some form of OA.[2] Currently, treatment for osteoarthritis is based on relieving pain and increasing mobility, but this treatment does not reverse the course of osteoarthritis, and the majority of patients with advanced osteoarthritis must undergo total joint replacement to maintain a normal life.[1] Arthroplasty imposes a significant burden of disease in health systems around the world. For example, a national public health program led by the Romanian Ministry of Public Health found that since the launch of the National Endoprosthesis Register in 2001, surveillance data up to 2022 showed that the total number of

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orthopedic surgeries in the country had accumulated to 1,557,247, of which joint replacement-related surgeries accounted for 253,498, or about 16.3% of the total number of surgeries. Of these, 253,498 were joint replacement-related surgeries, accounting for about 16.3% of the total number of surgeries.[3] Therefore, it is urgent to define as precisely as possible the predisposing mechanisms of osteoarthritis.

The brain is a major part of the central nervous system. There is a balance between centrally mediated neuronal pathways and neurotransmitters that connect the brain to the bone and enable the brain to regulate bone mass, a pathway known as the brain-bone axis,[4] and has received focused attention in recent research. Recent studies have shown that the brain can be centrally regulated via sympathetic and parasympathetic nerves to either inhibit or promote bone accumulation.[5,6] In addition, regulation of bone by brain-derived extracellular vesicles is also a pathway linking the brain to bone. In adult Alzheimer's disease (AD) mice, brain-derived extracellular vesicles mediated by MiR-483-5p exert anti-osteogenic, pro-adipose production, and pro-bone loss effects after translocation across the blood-brain barrier into bone tissue, promoting osteoporosis and bone marrow obesity.[7] As research progresses, osteoarthritis has been found to be one of the important downstream targets of the brain-bone axis in addition to bone density.

Current research exploring the link between the brain and osteoarthritis has focused on chronic pain. The hypothalamus of the brain regulates bone remodeling and structure through bone prostaglandin E2, which is associated with mechanical loading. Abnormal mechanical loading leads to elevated levels of prostaglandin E2, which activates sensory nerves and leads to low back pain.[8,9] Negative psychological traits have also been found to affect health outcomes in patients with chronic knee pain, which is accomplished by accelerating the aging of the patient's brain.[10] In addition to pain, the brain can have pathological effects on epiphyseal chondrocytes by inhibiting chondrocyte differentiation through modulation of the hypothalamic-pituitary-thyroid axis. However, most studies have not precisely delineated the brain to study the effects of specific structural alterations in the developmental process of osteoarthritis. On the other hand, the causal relationship between brain structure and OA has not yet been clarified, and whether it is possible to intervene in the process of OA through the brain is not yet known. This has resulted in a lack of clear targeting and little success in intervening in the progression of osteoarthritis through the brain-bone axis. It is therefore necessary to explore the potential causal links between specific functional areas of brain structure and OA.

Structural changes in brain regions include many heritable IDPs that can be measured by noninvasive magnetic resonance imaging (MRI) techniques and help resolve structural uncertainties. Diffusion-weighted magnetic resonance imaging (dMRI) is sensitive to neural axonal structure but relatively insensitive to myelin. When white matter tracts are highly structured, measured water diffusion is anisotropic, but becomes increasingly isotropic as neurons degenerate. Neuronal Orientation Diffusion and Density Imaging (NODDI) processes the diffusion signals into isotropic (ISOVF), restricted (ICVF), and blocked diffusion volume fractions, as well as an Orientation Diffusion Index (ODI). These IDPs can reflect in vivo microstructural properties. The ICVF can be used as a marker of the density of neural synapses (axons and dendrites) compared to healthy control white matter. In terms of white matter microstructure, an increase in ODI indicates axonal damage, demyelination, and a decrease in fiber orientation consistency, which negatively correlates with regional changes shown by FA. Diffusion tensor imaging (DTI) is used to characterize white matter and is commonly used in neuroscience research. FA is a diffusion index that can reflect white matter integrity, and mean diffusivity (MD) reflects the total water content of the tissue and expresses the total diffusion activity of water molecules and the average degree of molecular replacement. Decreased FA and increased MD are often interpreted as indicators of fiber bundle disruption and demyelination. In addition, common IDP structural metrics are GMV (in mm^3), surface area (SA, in mm^2), and cortical thickness (CT, in mm). It is therefore common practice to study physiologic and pathologic changes during disease progression by quantifying the brain's structural and functional integrity using these IDP metrics and determining whether or not the brain's structure and function are intact. This can aid in understanding the causes of disease onset or exacerbation.[11,12]

In brain-OA association studies, confounding factors such as substance use or living environment and lifestyle are often present, which may lead to biased results. Mendelian randomization (MR) has recently been widely used as an alternative method to assess the causality of observational data. It uses genetic variation as the instrumental variable (IV) of the study and is not subject to factors such as interference bias and confounders. This causality assessment provides a higher reference value for targeted therapies compared to traditional clinical studies. This is particularly important for

signaling interactions between brain and bone. This study intends to explore, through two-sample Mendelian randomization, whether brain structural parameters (eg, brain region volume or white matter integrity) have a direct causal effect on the development of OA and whether this exploration can provide a direction for new therapeutic targets for the brain-bone axis-mediated pathomechanisms of OA.

Materials and Methods

Data Source

Our study used STROBE-MR guidance to assess the integrity of the entire process (Table S1). A genome-wide association study, GWAS, conducted by Smith et al using 3,913 brain IDPs from 33,224 participants of European descent in the 2020 release of the UK Biobank (UKBB), provided the exposure data for this study. The GWAS summary statistics can be downloaded from the Oxford Genetics in Brain Imaging (BIG40) web browser (https://open.win.ox.ac.uk/ukbiobank/big40/). This GWAS dataset specifies functional structural metrics such as subcortical volume and tissue contrast. In addition, a recent genome-wide association study of single nucleotide polymorphisms (SNPs) associated with OA was considered as outcome data and included a total of 484,598 patients with OA (Ncase=39,515, Ncontrol=445,083), and this data is the most comprehensive and complete OA data available. In addition, we included 407,746 patients from the Firth-corrected OA cohort and 407,746 patients from the SPA-corrected OA dataset cohort from a genome-wide regression study in 2021. We confirmed these data from the publicly available GWAS catalog website (https://www.ebi.ac.uk/GWAS/downloads/summary-statistics, Accessed June 10, 2024). In addition, we included common smoking behaviors, alcohol consumption, and obesity as potential confounders and searched for SNPs associated with confounders on the PhenoScanner website (http://www.phenoscanner.medschl.cam.ac.uk/) and removed them to ensure the reliability of the results.

Selection of Instrumental Variables

To ensure the accuracy and robustness of the causal relationship between OA and IDPs showing the structural and functional integrity of the brain, we used the following steps to select IVs. In principle, the IVs used in MR analyses must satisfy three assumptions: the IVs must be correlated with the exposure; the IVs must be correlated with the outcome only through the exposure, with the confounding pathway unaffected by the genetic variants in the outcome; and the genetic variants do not directly affect the outcome but only indirectly affect the outcome through the exposure. First, cluster analyses were performed in the European 1000 Genomes Project Phase III reference panel (kb=10,000, r^2<0.001) to exclude SNPs with strong linkage disequilibrium (LD), thus reducing the occurrence of biased results. To ensure allelic concordance between exposure and outcome, SNPs with mismatched effect alleles, ambiguous strand orientation, or allele frequency discrepancies (>0.2) were excluded, guaranteeing that genetic effects reflect the same biological allele. Finally, to further quantify the strength of IV, we calculated the F statistic for each SNP individually and cumulatively by F= R2(N-k-1)/k(1-R2) to facilitate the exclusion of SNPs that could lead to unwarranted bias and multiplicity of significance. F statistic greater than 10 provides reasonable evidence that IV is a powerful tool.

MR Analysis

We conducted a two-sample MR analysis with genetic variance as IV to preliminarily investigate the causal correlation between exposure (brain structure) and outcome (OA). The primary analysis method was random-effects inverse variance weighting (IVW), and secondary analyses were weighted median and MR-Egger regression. An estimate of IVW can be obtained by calculating the slope of a weighted linear regression. The IVW method is recognized as the most reliable method when directed pleiotropy is not present in the SNPS. In addition, the weighted median consistently estimates causal effects when up to 50% of the genetic variation in the SNP is from null IVs. MR-Egger regression can also be utilized to assess potential associations if the genetic variance is not valid.

Sensitivity Analysis

Since there is no multidirectional hypothesis for MR, we performed sensitivity analyses to verify the reliability of the analysis. First, Cochran's Q test, MR-Egger regression, and IVW methods were utilized to assess IV heterogeneity. Additionally, we applied the MR-Egger intercept test to assess the horizontal multiplicity between IVW and the results; if the intercept value is closer to 0, the closer the MR regression model aspect is to IVW. Finally, to identify potentially influential SNPs and to assess the reliability of the results, we employed a "Leave-one-SNP-out" analysis, which avoids horizontal collapsing caused by a single SNP. We utilized funnel plots to assess heterogeneity among SNPS, and asymmetry was considered as an indicator of horizontal pleiotropy.

Meta-Analysis

In order to integrate all the positive results obtained from two-sample MR, to provide the highest level of evidence-based medicine and to validate the genetic findings, we performed a meta-analysis of the IVW results for OA and brain structures, a process implemented through STATA 12.0. Heterogeneity was tested using I^2, when I^2 was greater than 50%, heterogeneity existed and OR was calculated by the random effects model, otherwise OR was calculated by the fixed effects model.

Statistical Analysis

All data were analyzed with the "TwoSampleMR" package of R software (version 4.3.2). Originally developed in 1993 by Ross Ihaka and Robert Gentleman at the University of Auckland, New Zealand, the R language is now managed by the R Foundation for Statistical Computing, which coordinates the maintenance of the language with developers around the world through The Comprehensive R Archive Network and coordinated by developers worldwide. In the TwoSampleMR, $P < 0.05$ indicates that the difference between the results of the three statistical algorithms, Inverse variance weighted, MR Egger, and Weighted median, is statistically significant. In pleiotropy test, IV is considered horizontal horizontal multicollinearity between IVs existed when the MR-Egger regression intercept was non-zero and statistically significant ($p < 0.05$). In the heterogeneity test, $P>0.1$ indicates that there is no heterogeneity between groups.

Results

SNP Selection

Based on the above description, we extracted strong ($P < 5\times10^{-8}$), independent ($r2 < 0.001$) exposure-related independent SNPs as IVs. To avoid the bias of IV analysis, the F statistics for each SNPs were higher than 10. After harmonizing and eliminating SNPs with moderate allele frequencies and palindromic alleles, we ultimately screened 549 SNPs associated with IDPs of brain functional structures, as well as three sources of OA-associated SNPs. Ultimately, we utilized these significant SNPs for a two-sample Mendelian randomization analysis of brain structural parameters with OA (Figure 1).

Causal Relationship of Functional Brain Regions to OA

A total of 13 positive results existed when the functional brain region was the exposure and OA was the outcome. To ensure the robustness of the results, traits that showed a positive relationship with all three sources of OA were selected for the next step of the analysis. IVW results showed that 13 brain structural parameters had a significant causal relationship with OA. We demonstrate that increases in the limbic system, which is strongly related to cognitive function, were inversely correlated with the risk of OA. These increases included FA in the cingulate hippocampal gyrus, OD in the fornix, ISOVF, and OD in the stria terminalis. Increased volume of the inferior parietal lobule and the middle temporal gyrus, which are involved in processing higher-level sensory information, also had a protective effect against OA. For functional brain regions associated with proprioceptive and motor coordination, increased OD in the posterior thalamic radiation (R) was negatively associated with OA risk, whereas increased MO in the posterior thalamic radiation (L), ICVF in the cerebral peduncle, ISOVF in the anterior limb of the internal capsule, and OD in the medial thalamic tract exacerbated OA risk. Furthermore, we discovered an intriguing phenomenon: medial orbitofrontal volume was a risk factor for OA, whereas lateral orbitofrontal volume for the orbitofrontal lobe demonstrated a protective effect

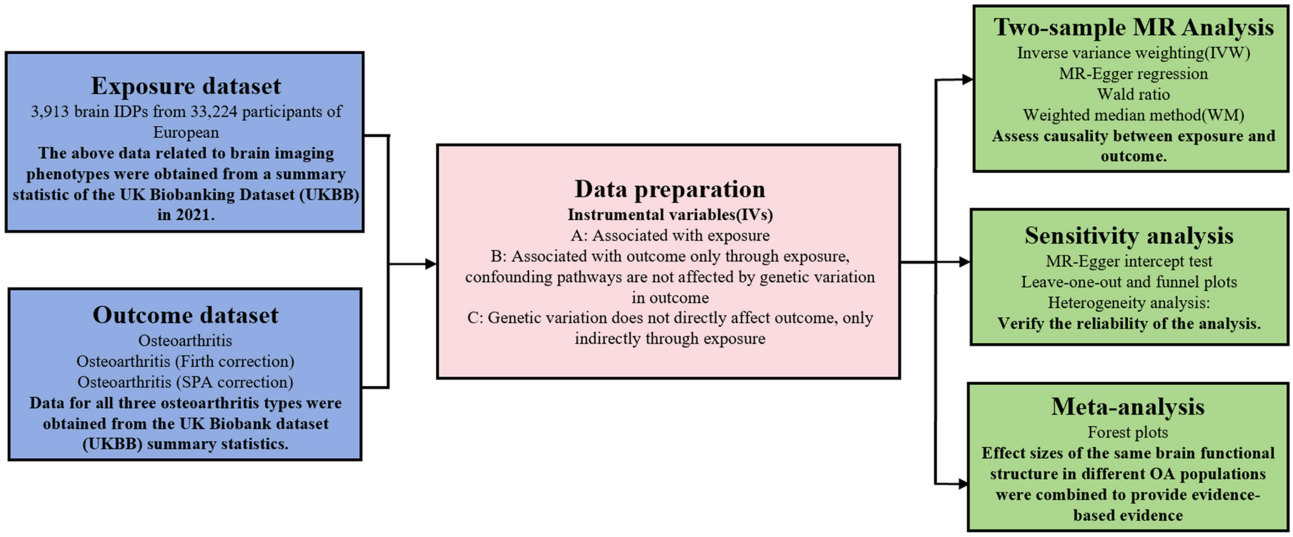

Figure 1 The flowchart of Mendelian randomization (MR).

against OA. The posterior thalamic radiation showed the same phenomenon. Table 1 displays specific P values along with confidence intervals. Results that added to the weighted median analysis supported the idea that the two were causally related (Table 1).

Table 1 Results of the Causal Associations Between OA and Brain Structure

Exposure	Outcome	SNP (n)	IVW		Weighted Median	
			P	OR (95%CI)	P	OR (95%CI)
Cingulum hippocampus (L)	OA (Firth correction)	7	0.003	0.83(0.73–0.94)	—	—
	OA (SPA correction)	7	0.003	0.83(0.73–0.94)	—	—
	OA	7	0.003	0.99(0.98–1.00)	0.008	0.99(0.98–1.00)
Posterior thalamic radiation (L)	OA (Firth correction)	3	0.002	1.36(1.11–1.65)	—	—
	OA (SPA correction)	3	0.002	1.36(1.11–1.65)	—	—
	OA	3	0.024	1.02(1.00–1.03)	0.041	1.02(1.00–1.03)
Cerebral peduncle (L)	OA (Firth correction)	27	0.015	1.08(1.02–1.16)	—	—
	OA (SPA correction)	27	0.015	1.08(1.02–1.16)	—	—
	OA	30	0.010	1.01(1.00–1.01)	—	—
Medial lemniscus (R)	OA (Firth correction)	3	0.016	1.27(1.05–1.54)	0.041	1.28(1.01–1.62)
	OA (SPA correction)	3	0.016	1.27(1.05–1.54)	0.047	1.28(1.00–1.63)
	OA	4	0.034	1.01(1.00–1.02)	—	—
Posterior thalamic radiation (R)	OA (Firth correction)	6	0.006	0.83(0.73–0.95)	—	—
	OA (SPA correction)	6	0.006	0.83(0.73–0.95)	—	—
	OA	6	0.047	0.99(0.98–1.00)	—	—
Fornix cres+Stria terminalis (L)	OA (Firth correction)	7	0.002	0.83(0.73–0.93)	—	—
	OA (SPA correction)	7	0.002	0.83(0.73–0.93)	—	—
	OA	10	0.004	0.99(0.98–1.00)	0.005	0.99(0.98–1.00)
Fornix	OA (Firth correction)	10	0.029	0.89(0.81–0.99)	0.001	0.82(0.73–0.93)
	OA (SPA correction)	10	0.030	0.89(0.81–0.99)	0.002	0.82(0.73–0.93)
	OA	12	0.039	0.99(0.99–1.00)	0.022	0.99(0.99–1.00)
Anterior limb of internal capsule	OA (Firth correction)	10	0.050	1.14(1.00–1.29)	—	—
	OA (SPA correction)	10	0.048	1.14(1.00–1.29)	—	—
	OA	12	0.033	1.01(1.00–1.01)	—	—

(*Continued*)

Table 1 (Continued).

Exposure	Outcome	SNP (n)	IVW		Weighted Median	
			P	OR (95%CI)	P	OR (95%CI)
lh volume lateralorbitofrontal	OA (Firth correction)	4	0.020	0.80(0.66–0.97)	—	—
	OA (SPA correction)	4	0.020	0.80(0.66–0.97)	—	—
	OA	6	0.038	0.99(0.98–1.00)	—	—
lh volume medialorbitofrontal	OA (Firth correction)	2	0.029	1.32(1.03–1.69)	—	—
	OA (SPA correction)	2	0.028	1.32(1.03–1.69)	—	—
	OA	2	0.024	1.02(1.00–1.04)	—	—
lh volume middletemporal	OA (Firth correction)	6	0.019	0.75(0.59–0.95)	0.021	0.78(0.64–0.96)
	OA (SPA correction)	6	0.018	0.75(0.59–0.95)	0.022	0.78(0.63–0.96)
	OA	8	0.029	0.98(0.97–1.00)	—	—
rh volume lateralorbitofrontal	OA (Firth correction)	9	0.001	0.82(0.73–0.92)	—	—
	OA (SPA correction)	9	0.001	0.82(0.73–0.92)	—	—
	OA	10	0.013	0.99(0.98–1.00)	0.049	0.99(0.98–1.00)
lh area inferiorparietal	OA (Firth correction)	7	0.027	0.87(0.77–0.98)	—	—
	OA (SPA correction)	7	0.027	0.87(0.77–0.98)	—	—
	OA	8	0.045	0.99(0.98–1.00)	—	—

Sensitivity Analysis

We carried out the sensitivity analysis test to further verify the veracity of the test findings. The IVW test revealed that, out of the 13 positive results, the only results with heterogeneity were the cerebral peduncle, lh volume middletemporal, and the three sources of OA ($P < 0.05$). The other results showed no heterogeneity. The pleiotropy between the IV and the results was also evaluated using the intercept of the MR-Egger regression analysis, and the findings showed that there was no horizontal pleiotropy (Table 2). Furthermore, no significant horizontal pleiotropy was observed, which suggested that there was no genetic variation heterogeneity based on the symmetry of the funnel plot. The current MR findings are largely robust, as the "leave-one-out" algorithm, with the exclusion of single SNPs, indicated that no single SNP significantly affects the possible causal link between brain structure and OA (Figures S1–S13).

Table 2 MR Estimates for the Association Between OA and Brain Structure

Exposure	Outcome	Heterogeneity		MR-Egger Regression		
		MR Egger	IVW	Intercept	SE	P
Cingulum hippocampus	OA (Firth correction)	0.707	0.751	0.014	0.020	0.516
	OA (SPA correction)	0.706	0.751	0.014	0.020	0.517
	OA	0.990	0.844	0.002	0.001	0.203
Posterior thalamic radiation	OA (Firth correction)	0.911	0.410	−0.079	0.059	0.410
	OA (SPA correction)	0.909	0.409	−0.079	0.059	0.410
	OA	0.504	0.723	−0.002	0.004	0.731
Cerebral peduncle	OA (Firth correction)	0.028	0.037	−0.001	0.007	0.900
	OA (SPA correction)	0.028	0.037	−0.001	0.007	0.919
	OA	0.034	0.044	0.000	0.000	0.779
Medial lemniscus	OA (Firth correction)	0.568	0.577	−0.093	0.106	0.541
	OA (SPA correction)	0.568	0.577	−0.093	0.106	0.541
	OA	0.388	0.586	0.001	0.006	0.858

(*Continued*)

Table 2 (Continued).

Exposure	Outcome	Heterogeneity		MR-Egger Regression		
		MR Egger	IVW	Intercept	SE	P
Posterior thalamic radiation	OA (Firth correction)	0.375	0.421	0.028	0.033	0.455
	OA (SPA correction)	0.375	0.421	0.028	0.034	0.456
	OA	0.346	0.482	0.000	0.002	0.912
Fornix cres+Stria terminalis	OA (Firth correction)	0.465	0.569	0.025	0.056	0.675
	OA (SPA correction)	0.465	0.568	0.025	0.056	0.675
	OA	0.864	0.773	0.004	0.003	0.224
Fornix	OA (Firth correction)	0.125	0.146	−0.012	0.018	0.509
	OA (SPA correction)	0.125	0.146	−0.012	0.018	0.508
	OA	0.749	0.815	0.000	0.001	0.821
Anterior limb of internal capsule	OA (Firth correction)	0.119	0.095	−0.020	0.018	0.291
	OA (SPA correction)	0.119	0.094	−0.020	0.018	0.287
	OA	0.485	0.413	−0.001	0.001	0.202
lh volume lateralorbitofrontal	OA (Firth correction)	0.354	0.294	−0.052	0.041	0.336
	OA (SPA correction)	0.353	0.294	−0.052	0.041	0.336
	OA	0.779	0.736	−0.002	0.002	0.374
lh volume medialorbitofrontal	OA (Firth correction)	0.521	—	NA	NA	NA
	OA (SPA correction)	0.523	—	NA	NA	NA
	OA	0.786	—	NA	NA	NA
lh volume middletemporal	OA (Firth correction)	0.009	0.017	0.010	0.034	0.778
	OA (SPA correction)	0.009	0.018	0.010	0.034	0.777
	OA	0.006	0.011	0.000	0.002	0.891
rh volume lateralorbitofrontal	OA (Firth correction)	0.292	0.362	−0.013	0.027	0.639
	OA (SPA correction)	0.292	0.362	−0.013	0.027	0.640
	OA	0.897	0.937	0.000	0.002	0.845
lh area inferiorparietal	OA (Firth correction)	0.843	0.713	−0.018	0.014	0.251
	OA (SPA correction)	0.843	0.713	−0.018	0.014	0.251
	OA	0.574	0.473	−0.001	0.001	0.225

Meta-Analysis

To find the overall conclusion, we ran a meta-analysis on the IVW data from the two-sample MR. We used a random-effects model to calculate the OR since all 13 positive results demonstrated statistical heterogeneity. This indicated that there was a correlation between the overall effects of brain anatomy on OA (Figure 2).

Discussion

In this study, we performed an unbiased assessment of the causal relationship between functional brain regions and OA using the new representative GWAS dataset. To effectively exclude the effects of other factors in traditional observational research, we independently examined the causal link between functional brain areas and OA in each of the 3 data sets. According to IVW results, 13 brain areas had causal associations with OA. For more robust results, only trait combinations with positive relationships from all three sources were analyzed. 8 brain regions were protective against OA, and 5 were linked to increased disease risk. Furthermore, meta - analysis combined the effect sizes of 13 positive outcomes, enhancing the study's evidence and reliability. Our study further explores the complex link between specific brain functions and OA's onset and progression, providing causal evidence highlighting the importance of early prevention strategies for OA advancement via the brain - bone axis.

Previous studies have shown that the brain is primarily involved in OA pain modulation. The hypothalamus detects pain in cases of osteoarthritis in the ankle by detecting the amount of PGE2 present in the bone.[8] Recent research has found strong associations between OA onset and brain - related disorders (besides pain). For example, Parkinson's

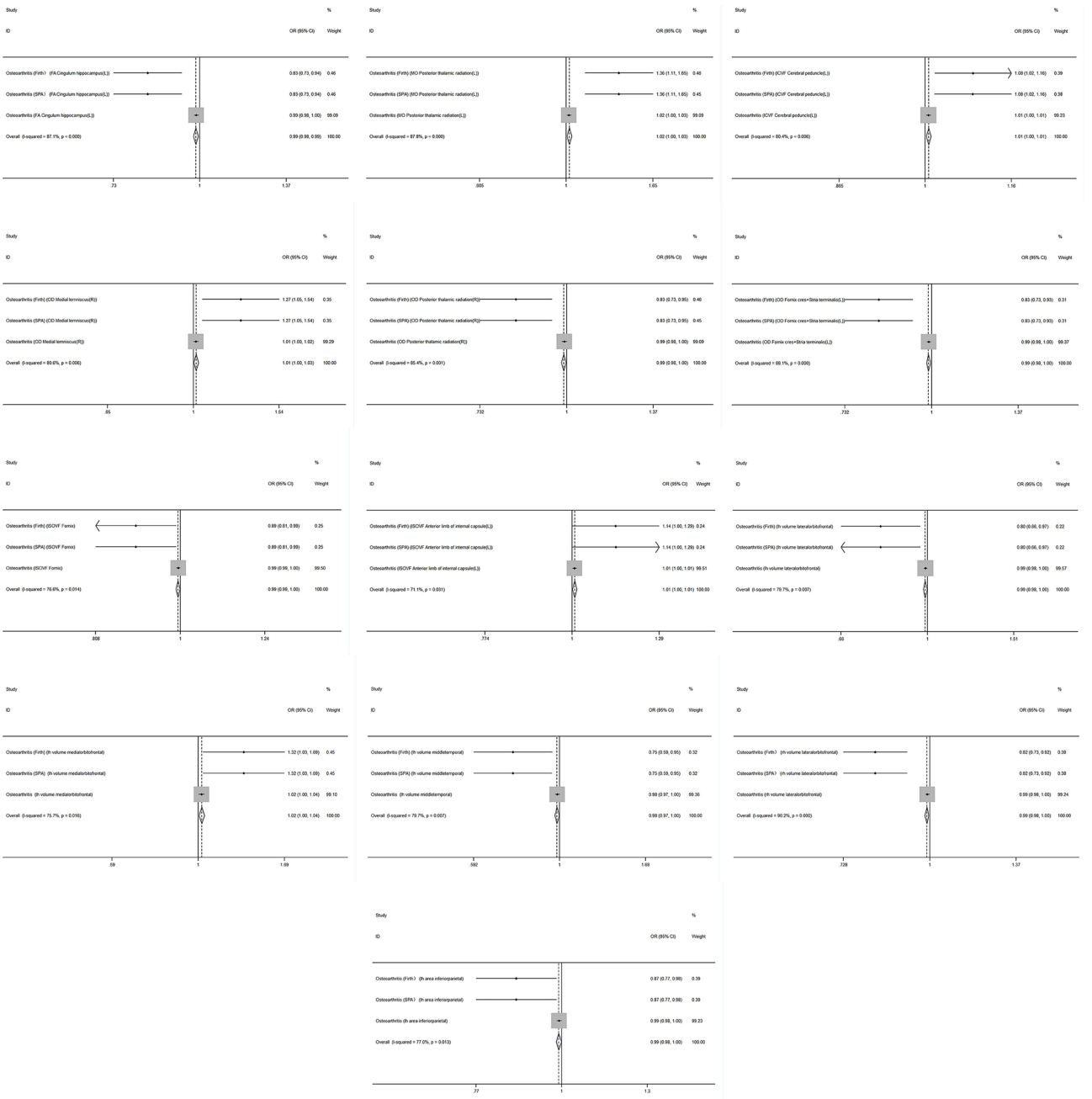

Figure 2 Meta-analysis of correlations between functional brain structures and osteoarthritis. Symbols and horizontal bars indicate combined ratio ratios and 95% confidence intervals from meta-analysis. Vertical lines indicate ratio ratios indicating no correlation (ROR=1).

disease patients have midbrain and striatum blood - brain barrier abnormalities. This may cause the brain's central inflammation to seep into the somatic circulation, initiating long-term, low-level systemic inflammation and exacerbating OA.[13] Unfortunately, few studies directly link specific brain structural subdivisions to OA. Interventions for OA progression along the brain - bone axis are only theoretical.[5,6,8] Therefore, it's crucial to understand how each brain region's structures contribute to OA development.

Our research showed that the structural integrity of the fornix, terminal stripe, and cingulate hippocampal gyrus was linked to a lower OA risk. In the brain's structure, all of the joint neocortical regions, where cortical projections create memories for later consolidation and retrieval, are related to the hippocampus.[14] The fornix is the main fiber bundle facilitating communication within the limbic system.[15] It links the nodes of the limbic circuits and is believed to be

important for cognition and situational memory recall.[16] In addition, the terminal stripe is a fiber bundle from the amygdala, and its transmission in the bed nuclei of the stria terminalis has been found to regulate memory consolidation via glucocorticoid-dependent and -non-dependent loops. Recent years' numerous investigations have revealed a significant epidemiological relationship between AD and orthopaedic diseases like osteoarthritis. This could be due to the same Wnt/β-catenin signaling pathway.[17] Nowadays, it is generally recognized that skeletal and neurodegenerative disorders are closely related to Wnt signaling system abnormalities.[18] A down-regulated pathway speeds up Amyloid precursor protein to Aβ conversion, increasing Aβ accumulation and amyloid pathology. This worsens Wnt signaling down - regulation, which is related to faster cartilage destruction and chondrocyte apoptosis.[19,20] According to Dengler - Crish CM et al's study on htau mice's bones and brains, when the Wnt/β-catenin signaling pathway is inhibited in bone tissue, AD mice have poor prognoses like decreased bone mineral density and impaired bone remodeling. This also worsens OA progression.[21] This suggests that promoting proper WNT pathway activation could be a new strategy to prevent OA onset by improving brain function. Moreover, other potential mechanisms have been found. Increasing evidence shows extracellular vesicles may also be important in the shared pathogenesis of OA and AD.[17] Extracellular vesicles (EVs), membrane-shaped organelles secreted by cells, participate in many physiological and pathological processes by delivering bioactive molecules and facilitating intercellular signal transduction and information exchange.[22] Research on brain-derived extracellular vesicles (B-EVs) in AD mice found that they have anti-osteogenic, pro-adipogenic, and pro-osteoporotic effects when they cross the blood-brain barrier to the bone tissues. This phenomenon was not seen in wild-type mice with normal brain function. It indicates that when brain function recovers, B-EVs' harmful effects on bone are alleviated and no longer promote osteoarthritis development.[7] The identification of these bioregulatory molecules implies a new communication link between bone and brain physiology, opening new prospects for OA prophylaxis and treatment.

Besides influencing cognitive function and being involved in learning and memory, the limbic system is crucial for generating and controlling emotional reactions. Damage to it disrupts the synchronization of mental processes, leading to impairments underlying certain mental diseases.[23] Many psychological conditions are significantly correlated with OA and are being researched for OA prevention. Barowsky S et al's cross-disease genomics data analysis showed that most risk genes were significantly expressed in six brain regions (cerebellar cortex, midbrain thalamic nucleus, striatum, amygdala, hippocampus, and neocortex). It also showed significant genome-wide genetic correlations and a common etiology between some mental disorders such as major depressive disorder (MDD) and osteoarthritis.[24] Mental illness may affect OA through common etiological paths related to stress, inflammation, immunological responses and shared genetic causes. A study on the link between mental illness and OA suggests that reversing MDD may protect against osteoarthritis.[25] The phenomenon may result from the innate immune system's sustained hyperactivation in depressed individuals.[26] These inflammatory mediators lead to the production and release of various protein - hydrolyzing enzymes, and the synthesis and breakdown of interstitial tissues in OA. IL-1β has been found to stimulate metalloproteinases (MMPs) production and induce Reactive oxygen species (including hydroxylated free radicals and peroxides) formation, which is harmful to cartilage.[27] When MDD improves, a protective effect against OA occurs as systemic immune activation or inflammatory response reduces. Also, pathological behaviors in mental health patients are related to abnormal brain activity. Once the disease shows, patients' actions and drugs may slow OA progression by affecting these brain structures.[28,29] Mendelian analysis shows that psychiatric drugs such as duloxetine, clozapine interact with common OA/MDD risk genes, which are highly enriched in the frontal cortex, anterior cingulate cortex (ACC), amygdala and other brain regions.[24] According to recent research, OA risk genes are also important for the pathophysiological activity in these areas. CRHR1, for example, which is a risk target for OA, has been found to interact with 19 drugs indicated for MDD and other mood disorders.[30,31] So, it's reasonable to assume that patients' drugs may treat mental illness by affecting certain brain genetic loci and may also slow OA progression by influencing common risk genes.

Interestingly, we found a correlation between OA improvement and bipolar disorder. Although not previously causally linked, a recent MR analysis strongly supports a causal genetic association between bipolar disorder and KOA risk.[1] Bipolar disorder (BD) is a periodic, chronic illness with manic, mixed or depressed episodes alternating with periods of mental stability.[32] Dysfunction of voltage-gated calcium channels is a drug target for neurological

disorders as it is associated with such disorders.[33] Cellular $Ca2^{+}$ channel malfunction is the primary cause of the disruption of $Ca2^{+}$ regulatory homeostasis that bipolar illness patients frequently exhibit clinically.[34] When Ca2+ endocytosis is inhibited, chondrocyte skeleton is stronger, less reactive to external mechanical forces and less likely to be damaged mechanically. This reduces resting Ca2+ concentration and slows OA progression.[35] This may explain BD's protective effects. Generally, when most mental illnesses recover, the abnormal brain regions also show favorable structural and functional states, reducing OA risk through various ways.

In our study, the right posterior thalamic amplitude, subparietal lobule, and middle temporal gyrus have protective effects against OA. The subparietal lobule and middle temporal gyrus mainly process high - level sensory information. A study on neurological correlates of potential food choice changes found that the likelihood of choosing to fast was positively related to brain activity in areas like the middle temporal gyrus and inferior parietal lobule.[36] If neuronal activity in these structures decreases due to atrophy or incompleteness, patients may become obese. Obesity - related uneven joint loading can cause arthropathological changes (abnormal joint structure loading, misaligned joints, muscle weakening), leading to altered gait kinematics that may shift loads to cartilage areas unadapted to chronic activity loads.[37] When cartilage cannot adapt to the changed chronic dynamic stress, degradation occurs and may accelerate OA onset.[38] In addition, improper mechanical loading prevents articular cartilage from regenerating and exacerbates OA.[37] Therefore, when the brain's middle temporal gyrus and inferior parietal lobule are structurally intact, OA can be greatly hindered.

Our investigation showed that the left posterior thalamic radiation, cerebral peduncle, medial thalamic tract, anterior limb of the internal capsule, and left medial orbitofrontal lobe promoted OA. Besides mental and neurological abnormalities, motor dysfunction is one of the most common results of structural brain injury. Proprioception is crucial for knee stability. Specific brain regions (prefrontal area, precentral gyrus, cingulate gyrus) respond differently when people sense knee position. Damage to these regions may affect knee proprioception and contribute to osteoarthritis.[39] The cerebral peduncles control somato - motor and sensory perception and are in the brainstem on both sides of the mid - central midbrain. The anterior limb of the internal capsule and the medial thalamic tract are important white matter structures for normal brain information transmission. Studies show that lesions of these brain structures often cause ataxia and related disorders.[40] Speech disorders, abnormal eye movements and gait are common in patients. Severe conditions like cerebral palsy can cause permanent loss of normal body movement ability. These impairments include joint abnormalities leading to abnormal movements, such as in knees and hips.[41–43] It has been shown that dynamic knee loading affects degenerative joint disease progression.[44] Joint alignment is a key factor in load distribution and is a potential biomechanical risk factor for osteoarthritis.[45] In knee varus or valgus, the knee center shifts due to joint deformity, causing the load to be biased medially or laterally across the knee. This redistributes joint strains and intensifies joint damage.[46,47] Therefore, for OA treatment, it's crucial to understand how these brain areas related to motor balance and coordination contribute to the disease's accelerated progression.

Additionally, our research had several interesting findings. The posterior thalamic radiation, a nerve fiber bundle from the caudolateral thalamic nucleus to the posterior parietal and occipital lobes via the posterior internal capsule, mediates upright body posture control and directional control.[48] In older people, decreased postural control often leads to a higher risk of joint injuries and more frequent falls.[49] This also explains our finding that left posterior thalamic radiation accelerates OA development. However, our study reported that right posterior thalamic radiation is protective against OA. But this study did not focus on exploring this protective effect, which is a knowledge gap that needs to be filled. Furthermore, a similar situation exists in the frontal lobes. Our research shows that different locations in the frontal lobes can have very different effects on osteoarthritis. The frontal lobe, which is important for complex cognitive processing and motor control, can lead to a traumatic gait and frontal lobe ataxia when injured.[40] This gait not only raises the risk of falls in the elderly and promotes OA development, but also tends to cause knee inversion or eversion, affecting knee load distribution and aggravating knee function deterioration in OA patients.[47,50] Consistent with previous research, an increase in the lateral orbitofrontal lobe area greatly slows OA progression; in the medial orbitofrontal lobe, the effect is the opposite. More research on brain region anatomical equivalents is needed to provide OA management and prevention recommendations.

In this study, the central regulatory role of the brain-bone axis in the development of OA was systematically revealed for the first time, which transformed a simple joint problem into a series of pathological progresses regulated by the nervous system, and broke through the insufficiency of the traditional OA research limited to the peripheral joint pathology. By demonstrating that the CNS accelerates the progression of OA through multidimensional pathways such as amplification of

pain signals, emotional-cognitive deficits, and reduction of motor control and regulation, this provides a new perspective for clinical practice: early intervention can be achieved by combining neuromodulatory and behavioral therapies in people with a high risk of OA in order to interrupt the disease progression before structural damage to the joints is sustained. Future studies need to further investigate the interaction between specific brain regions (eg, hippocampus, prefrontal cortex, thalamus, and inferior parietal lobe) and the joint microenvironment, and to develop clinical strategies based on neural biomarkers for the prevention and treatment of OA.

Our investigation used the two-sample MR approach to determine the causal relationship between brain structural parameters and OA, which has several advantages. Firstly, for result reliability, we used multiple methods in research and validation. MR analysis found potential links, and meta - analysis enhanced precision. Secondly, we selected exposures from wide - range GWAS data of the Integrated Brain IDP for a more comprehensive study. Thirdly, using three outcome data, the final positive outcome was defined as positive for all three. Omitting non-overlapping information ensured evaluation validity, and sensitivity analysis confirmed accuracy. Our research offers more precise guidance for investigating intervention of OA by clarifying the relationship between specific brain areas and the disease.

Our study has limitations. First, restricting the study to Europeans reduced population - stratification bias, but the study is not generalizable to other races. Second, we only studied brain structural parameters, not exploring the impact of substance - metabolism changes on OA progression or the effects of OA processes on these regions. Third, two - sample MR analysis only examines the linear relationship between exposure and outcome, so a nonlinear analysis could not be done. Finally, this study did not discuss bidirectional effects, and it is still possible that there is pleiotropy of participation, and it is important to refine bidirectional MR analyses.

Conclusions

Our meta - analysis and two - sample MR analysis revealed a strong statistical causal link between 13 brain structures and OA. This finding may clarify how changes in these brain structures impact OA development, providing new insights and suggestions for brain-bone axis intervention and OA prevention. Moreover, our results explore the possible influence of brain structural lesions on OA at the neuroimaging level, opening up new opportunities for OA early detection and prevention.

Abbreviations

ACC, Anterior cingulate cortex; AD, Alzheimer's disease; BD, Bipolar disorder; B-EVs, Brain-derived extracellular vesicles; BIG40, Brain Imaging; dMRI, Diffusion-weighted magnetic resonance imaging; DTI, Diffusion tensor imaging; EVs, Extracellular vesicles; FA, Fractional anisotropy; ICVF, Intracellular Volume Fraction; IDPs, Imaging-derived phenotypes; ISOVF, Isotropic Volume Fraction; IV, Instrumental variable; IVW, inverse variance weighting; LD, Linkage disequilibrium; MD, Mean diffusivity; MDD, Major depressive disorder; MMPs, Metalloproteinases; MR, Mendelian randomization; MRI, Magnetic resonance imaging; NODDI, Neuronal Orientation Diffusion and Density Imaging; OA, Osteoarthritis; OD, Orientation Diffusion; SNPs, Single nucleotide polymorphisms; UKBB, UK Biobank.

Data Sharing Statement

The datasets generated during and analysed during the current study are available in the Oxford Genetics in Brain Imaging (BIG40) web browser and GWAS catalog website, https://open.win.ox.ac.uk/ukbiobank/big40 and https://www.ebi.ac.uk/gwas/downloads.

Ethics Approval and Informed Consent

The data used in this study were obtained from the UK Biobank and the European Population Database, which are freely available, and therefore the Second Hospital of Shanxi Medical University waived the requirement for ethical review.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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