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ORIGINAL RESEARCH

Resting-State Functional MRI Reveals Altered Seed-Based Connectivity in Diabetic Osteoporosis Patients

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Background: Diabetic osteoporosis (DOP) can cause abnormal brain neural activity, but its mechanism is still unclear. This study aims to further explore the abnormal functional connectivity between different brain regions based on the team's previous research.

Methods: Resting-state functional magnetic resonance imaging (rs-fMRI) data were obtained from 14 participants diagnosed with type 2 diabetes mellitus (T2DM) and osteoporosis. For comparison, data from 13 T2DM patients without osteoporosis were analyzed. The seed regions for functional connectivity (FC) analysis were chosen according to brain areas previously reported to exhibit abnormal regional homogeneity (ReHo).

Results: DOP patients exhibited significantly decreased BMD, T-scores, MoCA scores, and osteocalcin (OC) levels compared to controls ($p<0.05$). FC analysis revealed: 1) Reduced connectivity between the left middle temporal gyrus (increased ReHo) and middle occipital gyrus; 2) Enhanced connectivity between the right angular gyrus (increased ReHo) and left Rolandic operculum; 3) Weakened the left precuneus (increased ReHo) and right superior/left middle frontal gyri. These alterations correlated with deficits in visual processing, working memory, and executive function.

Conclusion: Distinct FC reorganization in DOP patients reflects synergistic effects of metabolic and skeletal pathologies on neural networks, potentially mediating cognitive decline through visual pathway disruption and prefrontal-default mode network decoupling. The findings highlight neuroimaging biomarkers for metabolic bone disease-related cognitive disorders.

Keywords: diabetic osteoporosis, functional connectivity, regional homogeneity, bone mineral density

Introduction

Diabetic osteoporosis (DOP), a critical metabolic bone complication of diabetes, is clinically characterized by a significant reduction in bone mineral density (BMD), degenerative changes in bone microstructure, and a marked increase in fracture risk.[1,2] Against the backdrop of the continuously rising global prevalence of diabetes (9.3% in 2019, projected to increase to 10.9% by 2045[3]), the disease burden of DOP is particularly prominent: approximately 10 million osteoporotic fractures occur worldwide annually, resulting in 5.8 million Disability-Adjusted Life Years (DALYs) lost, accounting for 0.83% of the total burden of non-communicable diseases.[4] Studies in the Chinese population further reveal a gender disparity in the prevalence of osteoporosis among type 2 diabetes patients, with rates of 44.8% in females and 37.0% in males,[5] highlighting the close association between metabolic abnormalities and bone homeostasis imbalance. At the molecular mechanism level, the high-glucose microenvironment disrupts bone metabolic homeostasis through a multi-dimensional signaling network: first, diabetes-related inflammation inhibits osteoblast differentiation and

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accelerates osteoblast apoptosis via bidirectional regulatory mechanisms, directly impairing bone formation capacity;[6,7] second, the peroxisome proliferator-activated receptor γ (PPAR-γ) regulatory network, serving as a shared hub for glucose and bone metabolism, not only contributes to the development of insulin resistance,[8] but also influences bone remodeling by regulating the expression of osteogenic differentiation marker genes.[9] More integratively, the receptor activator of nuclear factor-κB ligand (RANKL) signaling pathway exhibits trans-organ regulatory properties—it exacerbates bone resorption hyperactivity by mediating osteoclast differentiation and triggers systemic inflammation while worsening insulin resistance by activating the NF-κB signaling axis in the liver,[10] thus elucidating the molecular interactive mechanisms underlying the comorbidity of type 2 diabetes and osteoporosis.

Diabetes, as a well-established neurometabolic risk factor, has been widely confirmed to exhibit clinical relevance to central nervous system dysfunction, manifesting as a continuum of neurodegenerative changes ranging from mild cognitive decline to full-blown dementia.[11] Mechanistic studies indicate that the abnormal accumulation of advanced glycation end products (AGEs) may exacerbate neural injury through multiple pathophysiological cascades, including imbalanced proinflammatory cytokine release, disruption of redox homeostasis, accumulation of pathological protein cross-linking, impairment of brain insulin signaling transduction, and metabolic network dysregulation.[12] Neuroimaging evidence reveals that patients with type 2 diabetes display characteristic alterations in resting-state neural activity in key brain regions such as the left prefrontal cortex, right angular gyrus, and left caudate nucleus, with these abnormal patterns showing a significant negative correlation with cognitive function scores.[13] Notably, a bidirectional vicious cycle exists between cognitive impairment and bone metabolic disorders: dementia patients not only exhibit a significantly increased risk of osteoporosis and hip fractures but also demonstrate progressive decreases in BMD detectable in the early stages of Alzheimer's disease, with the magnitude of decline positively correlated with the degree of cognitive impairment.[14] Epidemiological data show that approximately 40% of hip fracture patients have a history of dementia.[15] Based on our team's previously identified bone-brain axis regulatory mechanism,[16] we propose an innovative hypothesis: in the population of patients with DOP, particularly those with comorbid cognitive impairment, characteristic reorganization of functional neural network connections may occur, and this reprogramming pattern of neural functional networks could serve as a potential biomarker for cross-system metabolic disorders.

Functional connectivity (FC), which quantifies the temporal synchronization of blood-oxygen-level-dependent (BOLD) signals across spatially separated brain regions, is based on the core assumption that brain regions exhibiting coordinated neural activity form functionally integrated networks. Growing evidence indicates that FC holds promise as a diagnostic biomarker for identifying cognitive impairment associated with Alzheimer's disease (AD).[17] Studies have shown that patients with type 2 diabetes mellitus (T2DM) exhibit significantly reduced FC between the posterior cingulate cortex and widespread brain regions.[18] Changes in resting-state FC observed via functional magnetic resonance imaging (fMRI) have been proposed as biomarkers for bone trauma-induced processes during fracture healing in musculoskeletal pathological conditions.[19] However, research on resting-state brain functional connectivity in patients with DOP remains largely unexplored.

Previous research by our team[16] has demonstrated that patients with DOP exhibit abnormal Regional Homogeneity (ReHo) in specific brain regions. This discrepancy reflects the characteristic coordinated activity of neuronal populations in local brain areas, which may be associated with information processing within local neural circuits, such as alterations in neuronal excitability or synaptic transmission efficiency. Importantly, brain regions do not function in isolation; instead, they form highly complex and interwoven neural networks through intricate connections, collectively supporting complex cognitive, emotional, and behavioral functions. Building on this, the present study uses the abnormal brain regions identified in our prior work[16] as seed regions to investigate functional connectivity abnormalities in the brain networks of DOP patients, particularly those with comorbid cognitive impairment. These findings are expected to provide novel insights into the neurophysiological mechanisms underlying DOP-related brain functional abnormalities.

Methods

Subjects

The research protocol received ethical approval from the Institutional Review Boards of both Universiti Teknologi Mara and the Second Affiliated Hospital of Shandong First Medical University, with written informed consent obtained from

all participants prior to their involvement in the study. This study was conducted in accordance with the Declaration of Helsinki. The subjects of this study were from the research group's database,[16] and a total of 29 T2DM patients were included, 15 patients in the DOP group (average age 58.33 ± 4.63 years), including 5 males and 10 female patients; the control group consisted of 14 T2DM patients without osteoporosis (average age 56.00 ± 4.22 years), including 6 males and 8 female patients. The criteria for the diagnosis of diabetes was:[20] the fasting plasma glucose (FPG)≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8h. The 2-h plasma glucose (2-h PG)≥200mg/dL during a 75-g oral glucose tolerance test (OGTT). Glycosylated hemoglobinA1c (HbA1c)≥6.5%(48 mmol/mol). A random plasma glucose ≥200 mg/dL (11.1 mmol/L).

The demographic characteristics of both groups, including gender distribution, age range, and educational background, were carefully balanced. Comprehensive participant information has been previously documented in our earlier publication.[16]

General Information and Cognitive Assessment

A comprehensive clinical evaluation protocol was systematically conducted by qualified medical personnel, encompassing anthropometric measurements (height, weight, and BMI calculation) and biochemical analyses (HbA1c and serum osteocalcin levels). Cognitive function was assessed using the standardized Montreal Cognitive Assessment (MoCA), a well-validated screening tool with demonstrated sensitivity in detecting Mild Cognitive Impairment.[21] The MoCA assesses several cognitive domains. These are Visuospatial/Executive, Naming, Memory, Attention, Language, Abstraction, Delayed Recall and Orientation (to time and place). Following established scoring criteria, participants achieving a total score of 26 or higher were classified as cognitively normal, with an additional point awarded to individuals having fewer than 12 years of formal education. All cognitive assessments were administered by certified professionals in a controlled environment to ensure testing validity.

Bone Mineral Density (BMD)

The BMD of lumbar vertebrae (L1-L4) was measured by dual-energy X-ray absorptiometry (Horizon W, Hologic Inc, US), and then averaged. Based on the diagnostic criteria established by the World Health Organization Working Group on osteoporosis,[22] BMD status was categorized as follows: normal BMD (T-score ≥ −1.0 at one or more measurement sites), osteopenia (T-score between −2.5 and −1.0), and osteoporosis (T-score ≤ −2.5). The enrolled study participants were carefully selected DOP patients who fulfilled the diagnostic requirements for osteoporosis according to these standardized criteria.

MRI Data Acquisition

Magnetic resonance imaging acquisitions were conducted on a 3T Discovery MR750 scanner (GE Healthcare, Waukesha, WI, USA) utilizing an eight-channel phased-array receiver coil. Rigorous motion control measures were implemented, including foam padding for head immobilization and noise-reducing headphones to mitigate acoustic interference. Scanning protocols required participants to maintain an eyes-closed, wakeful resting state while refraining from systematic mental processes. Preliminary anatomical imaging served to exclude participants with structural brain abnormalities, such as space-occupying lesions, ischemic changes, or hemorrhagic foci. High-resolution structural data were obtained through a T1-weighted three-dimensional BRAVO sequence, while functional data collection employed an echo-planar imaging protocol with gradient-echo acquisition. Detailed imaging parameters have been previously reported in the research team's methodological publications.[16]

Data Preprocessing and FC Analysis

Functional image preprocessing and functional connectivity analysis were performed using the data processing assistant in the resting-state functional magnetic resonance imaging (rs-fMRI) toolbox (DPABI)[23] (DPABI, http://rfmri.org/dpabiV6.0_210501) and SPM12 (www.fl.ion.ucl.ac.uk/spm) software. The initial 10 time points were excluded from analysis to account for magnetic field stabilization and participant adaptation. Rigorous motion correction criteria were applied, excluding participants demonstrating translational movement exceeding 2.0 mm or rotational displacement

greater than 2.0° in any direction during the fMRI acquisition, resulting in the removal of two subjects from subsequent analyses. The remaining functional images underwent spatial preprocessing, including realignment to a reference volume, normalization to the standardized Montreal Neurological Institute (MNI) template space with 3mm isotropic voxel resolution, and spatial smoothing using an 8mm full-width at half-maximum Gaussian kernel.

For functional connectivity analysis, seed regions were identified based on areas demonstrating statistically significant ReHo values. The resting-state fMRI data underwent preprocessing with temporal band-pass filtering (0.01–0.08 hz) and linear detrending to remove low-frequency drift. Seed reference time courses were generated by computing the mean temporal signal across all voxels within each defined seed region. To normalize the distribution of correlation coefficients, Fisher's z-transformation was applied to convert Pearson's r values into z-scores, thereby enabling parametric statistical analysis.

Statistical Analysis

Statistical analyses were conducted using SPSS Statistics software (version 23.0, IBM Corp). Categorical demographic variables, including gender distribution, were compared between groups using Pearson's chi-square test. The normality assumption for continuous variables was assessed through the Kolmogorov-Smirnov test within each study group. Based on the distribution characteristics, parametric comparisons were performed using independent-samples *t*-test, while non-parametric analyses were conducted with the Mann-Whitney *U*-test to evaluate group differences between DOP patients and controls. A significance threshold of $p = 0.05$ was established for all statistical tests.

Results

Demographics

Independent samples *t*-test analysis revealed statistically significant between-group differences in several key parameters. The DOP group demonstrated significantly decreased mean values for bone mineral density (BMD average), T-scores, MoCA scores, and osteocalcin (OC) levels compared to the control group ($p < 0.05$). However, no significant intergroup variations were observed in demographic characteristics, including age distribution, gender proportion, anthropometric measures (height, weight, and BMI), glycemic control (HbA1c levels), and educational attainment (all $p > 0.05$), as detailed in Table 1.

Altered Interregional Functional Connectivity

The selection of functional connectivity seed points was based on previous functional MRI studies on regional homogeneity in DOP patients,[16] five different clusters were respectively defined as the seeds to investigate the effects of abnormal intrinsic activity on FC. Compared to the Control group, patients with DOP had significantly higher ReHo values in the left middle temporal (MTG, ROI 1), right superior occipital (SOG, ROI 2), right superior parietal (SPL, ROI 3), right angular (AG, ROI 4) and left Precuneus (PE, ROI 5). Comparative analysis revealed no significant

Table 1 Demographic, Clinical, and Cognitive Data

	Age (Years)	Sex (Male/Female)	HbA1c (%)	Education (Years)	BMI (kg/m2)	Weight (Kg)	Height (CM)	BMD AVG	T AVG	MoCA	OC
DOP	58.33±4.63	5/10	8.24±1.21	9.93±2.40	23.90±3.42	62.46±9.83	161.60±6.10	0.77 (0.70, 0.83)	−2.74±0.66	21.67±2.47	23.53 (22.05, 24.81)
CON	56.00±4.22	6/8	8.64±1.63	11.86±3.21	26.21±3.34	68.32±5.35	163.43±5.14	1.04 (1.02, 1.12)	−0.01±0.58	25.64±2.65	29.94 (26.97, 32.79)
P value	0.169	0.597[a]	0.463	0.077	0.077	0.059	0.392	0.000*[b]	0.000*	0.000*	0.000*[b]

Notes: Statistical significance was defined as *p < 0.05. Data presentation followed established conventions: categorical variables as frequency counts (n), normally distributed continuous variables as mean ± standard deviation, and non-normally distributed variables as median (interquartile range). [a] Gender comparisons were analyzed using Pearson's chi-square test. [b] Non-parametric analyses were performed using the Mann-Whitney *U*-test.

Abbreviations: DOP, Diabetic Osteoporosis; Con, Control group (type 2 diabetes mellitus patients without osteoporosis); BMI, Body Mass Index; BMD, Bone Mineral Density; MoCA, Montreal Cognitive Assessment; OC, Osteocalcin.

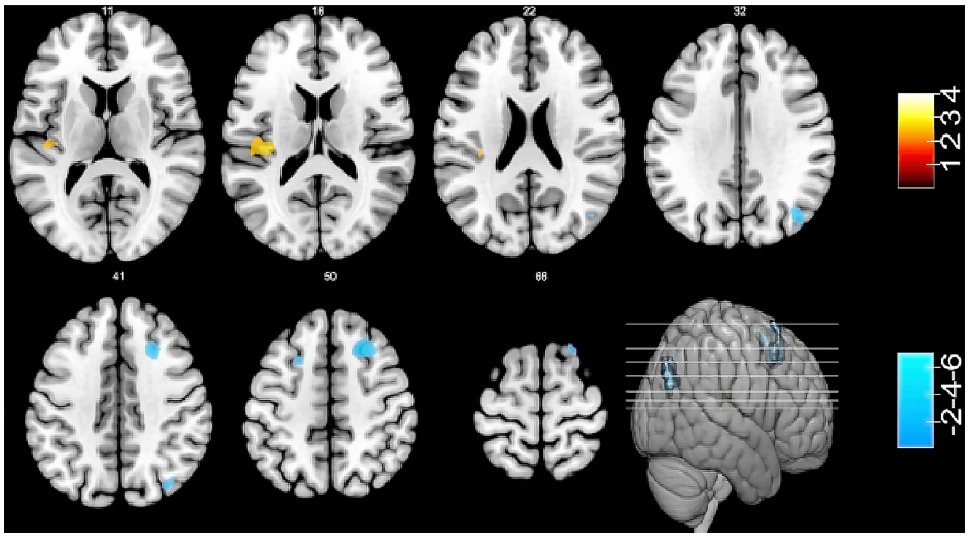

Figure 1 Functional connectivity patterns from seed points to voxels are visualized through a chromatic encoding system. Enhanced connectivity is represented by warm spectral hues (yellow), while reduced connectivity is depicted using cool spectral tones (blue). The colorimetric scale corresponds to the statistical t-values derived from intergroup comparisons, with the chromatic intensity quantitatively reflecting the magnitude of connectivity differences.

reduction in ReHo values in DOP patients relative to the control group. The ReHo values of the left MTG showed positive correlation with the average BMD (BMD AVG) and average T scores (T AVG); The ReHo values of the right SOG and right SPL showed negative correlation with MoCA scores; The ReHo values of right SPL showed negative correlation with OC. Functional connectivity analysis identified distinct patterns of neural network alterations: (1) decreased FC between the left middle temporal gyrus (higher ReHo, ROI 1) and right middle occipital gyrus; (2) increased FC between the right angular gyrus (higher ReHo, ROI 4) and left Rolandic operculum; (3) reduced FC between the left precuneus (higher ReHo, ROI 5) and both the right superior frontal gyrus and left middle frontal gyrus. Notably, seeds located in the right superior occipital gyrus and right superior parietal lobule (ROIs 2–3) demonstrated no significant FC alterations. All findings, illustrated in Figure 1 and detailed in Table 2, were corrected for multiple comparisons using topological false discovery rate (FDR) at a significance threshold of $p < 0.05$.

Table 2 Brain Regions Exhibiting Intergroup Differences in Seed-Based FC

Brain Region	MNI Coordinates			T value	Cluster Size
	X	Y	Z		
Rolandic_Oper_L (AAL)	−36	−27	18	3.7147	39
Occipital_Mid_R (AAL)	39	−69	30	−3.5492	64
Frontal_Sup_R (AAL)	21	24	45	−6.0751	93
Frontal_Mid_L (AAL)	−27	24	57	−3.2706	36

Abbreviations: L, left hemisphere; R, right hemisphere; AAL, Automated Anatomical Labeling atlas; MNI, Montreal Neurological Institute coordinate system; Cluster threshold: >35 voxels.

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Discussion

The current investigation employed regions exhibiting significant ReHo variations as seed points for functional connectivity analysis. The analysis revealed distinct patterns of neural network alterations, characterized by enhanced functional connectivity in the Rolandic operculum and reduced connectivity in several cortical regions, including the right middle occipital gyrus, right superior frontal gyrus, and left middle frontal gyrus.

As a critical hub for multimodal integration, the Rolandic operculum (ROL) engages in emotion regulation, sensorimotor integration, and self-awareness maintenance through its involvement in the cingulate-opercular network. Neuroimaging studies have confirmed its anatomical connectivity with the insular cortex and its role in integrating exteroceptive and interoceptive signals, which underpin cognitive functions.[24–27] Notably, this study revealed significantly enhanced functional connectivity between the right angular gyrus (ROI 4) and left ROL in DOP patients. Such interhemispheric connectivity abnormalities may reflect compensatory mechanisms following impaired brain network activity, aligning pathologically with prior findings in T2DM cohorts that demonstrated default mode network dysfunction, particularly in the superior temporal gyrus/ROL complex, and glucose metabolism-related language deficits.[28–30] Further evidence indicates that ROL lesions selectively impair the recognition of happy, fearful, and sad facial expressions, suggesting its coordinated regulation of social cognition with the insula and middle frontal gyrus (MFG).[31] Concurrently, reduced low-frequency amplitude (ALFF) in this region during executive control tasks correlates with global cognitive decline in chronic small vessel disease (cSVD) patients, reinforcing its role in modulating cognitive processing efficiency.[32] Moreover, the ROL participates in cognitive-motor integration via its functional circuit involving the cingulate cortex, insula, and supplementary motor area, where its white matter connectivity with premotor cortex potentially mediates language fluency and other higher-order functions.[33] Collectively, these findings highlight that ROL-mediated cross-network connectivity reorganization may serve as a crucial biomarker for metabolic disorder-related cognitive impairment.

The occipital lobe, a core region housing the primary visual cortex, plays a critical role in visual information processing, intercortical communication, and facial emotion recognition. Its functional synergy with the parietal lobe is essential for spatiotemporal processing and visual attention regulation.[34,35] Dysfunction in the occipital lobe may lead to visual pathway abnormalities, impairing environmental perception and visual signal integration.[36] This study observed diminished functional connectivity between the middle occipital gyrus and the left middle temporal region (ROI 1) in DOP patients, suggesting compromised integrity of the visual pathway. Such occipital abnormalities likely reflect latent visual deficits, aligning with the pathological mechanisms of complications like diabetic retinopathy during T2DM progression.[37] Clinical studies further revealed independent associations between reduced BMD, fracture risk, and cognitive decline in female populations, highlighting systemic interactions between metabolic dysregulation and neural degeneration.[38] Additionally, reduced functional connectivity between the right superior occipital gyrus and postcentral gyrus, as well as between the right middle occipital gyrus and left angular gyrus, correlated significantly with subjective cognitive decline (SCD), indicating that occipital-parietal/frontal network connectivity serves as a neural substrate for sustaining attention and executive functions.[39] Collectively, osteoporotic changes may exacerbate visual pathway degeneration in T2DM patients, reflecting intricate cross-system interactions among metabolic, skeletal, and neural systems.

This study revealed significantly weakened functional connectivity between the left precuneus (ROI 5, showing increased regional homogeneity) and the right superior frontal gyrus (SFG) as well as the left middle frontal gyrus (MFG) in DOP patients. The SFG, a hub for advanced cognitive operations such as working memory, attentional control, and decision-making, exhibits functional specialization: its lateral subdivision supports working memory execution, the medial portion integrates with the default mode network, and the posterior segment mediates motor functions via the supplementary motor area.[40,41] Metabolic imaging studies demonstrated reduced glucose metabolism in the precuneus and right SFG of diabetic patients,[42] while diminished resting-state connectivity among the left insula, right precuneus, and right SFG in T2DM patients with mild cognitive impairment further corroborates this network impairment.[43] The observed SFG-precuneus decoupling in DOP patients suggests working memory deficits, aligning with prior evidence that glycemic dysregulation disrupts working memory performance and osteoporosis elevates cognitive risk.[44,45]

Moreover, SFG-related dynamic connectivity abnormalities are implicated in neurodegenerative disorders: elevated regional homogeneity in the right SFG of Parkinson's disease with rapid eye movement sleep behavior disorder (PD-RBD) may reflect compensatory reorganization of cognitive control,[46] whereas reduced dynamic connectivity variability between the SFG and frontoparietal control network (CEN) correlates with global cognitive decline in Alzheimer's disease (AD) patients.[47] Notably, SFG activation during motor tasks (eg, grip imagination) and its functional reorganization with motor cortex following brain-computer interface (BCI) training underscore its role in cognitive-motor coupling.[48] The widespread SFG connectivity abnormalities in DOP patients may thus impair both cognitive and sensorimotor integration. Collectively, SFG network disruption may serve as a critical biomarker of metabolic-skeletal interactions on central neural circuitry.

MFG, a critical hub bridging the dorsal attention network (mediating endogenous attentional reorientation) and ventral attention network (processing exogenous stimuli),[49–51] forms a prefrontal core network with the right cingulate gyrus and left MFG to coordinate advanced cognitive functions such as attentional control, working memory, and metabolic regulation.[52,53] This study observed weakened functional connectivity between the left MFG and left precuneus in DOP patients, suggesting glucose metabolism disturbances may underlie attentional network impairment, potentially compounded by bone-brain crosstalk. MFG neural activity is closely linked to cerebral glucose metabolic patterns,[54] while dysregulation of the bone-derived biomarker osteocalcin (modulating cognitive pathways)—evidenced by reversible anxiety and memory deficits in osteocalcin-deficient mice—highlights skeletal metabolic disruption as a contributor to cognitive dysfunction via neural or systemic pathways.[55–57] Neuroanatomical studies reveal functional specialization within MFG: its dorsolateral (DLPFC) and orbitofrontal subdivisions regulate executive control and emotional processing, respectively, with reduced gray matter volume (GMV) correlating with executive deficits (eg, impaired task-switching in depressed patients).[58,59] Furthermore, MFG dynamically balances attention networks through connectivity with the anterior cingulate cortex (ACC), parietal regions, and temporal lobes, where transcranial magnetic stimulation (TMS) targeting MFG enhances cognitive control.[60] Its negative functional connectivity with the posterior cingulate cortex (PCC) and precuneus may suppress internal mentation to sustain task focus.[61] Collectively, MFG connectivity abnormalities in DOP patients may reflect synergistic effects of metabolic dysregulation and osteogenic signaling disturbances, serving as a multidimensional marker of cognitive pathophysiology.

Limitations

This investigation has several limitations that merit formal acknowledgment. First, statistical power may be constrained by the relatively modest sample size, potentially limiting generalizability; future research should validate and extend findings using larger cohorts with longitudinal follow-up designs. Second, exclusive reliance on seed-based functional connectivity analysis restricts the ability to capture the complexity of neural networks in information processing. To address this, integrating whole-brain connectivity mapping with graph-theoretical metrics (eg, nodal efficiency, modularity) would better characterize large-scale network dynamics and global topological properties beyond regional dependencies. Third, the lack of an osteoporosis-only control group—a consequence of the clinical difficulty in recruiting osteoporosis patients with preserved metabolic function—compromises mechanistic inference; therefore, subsequent studies should incorporate both osteoporosis-only and healthy control groups to discriminate disease-specific effects. Finally, while exclusion criteria controlled for major confounders, detailed documentation of diabetes medication subtypes (eg, insulin vs oral hypoglycemics) and subclinical vascular complications remained unanalyzed. Future research should incorporate comprehensive pharmacological profiling and advanced vascular imaging to characterize these potential confounders systematically.

Conclusion

This study uses resting-state functional magnetic resonance imaging to characterize abnormal functional connectivity in T2DM patients with DOP, identifying: 1) enhanced Rolandic operculum–angular gyrus connectivity (potential compensatory cognitive-motor integration), 2) reduced occipital-temporal pathway integrity (visual processing deficits), and 3) prefrontal (superior/middle frontal gyri)–precuneus network decoupling (working memory decline). These alterations correlate with decreased BMD, lower OC values, and lower MoCA scores, indicating synergistic effects of metabolic/

skeletal pathologies on neural disintegration. While the cross-sectional design limits causal inference and marker specificity needs validation, findings highlight neural mechanisms linking metabolic bone disease to cognitive impairment. Future directions include longitudinal studies, multi-disease cohort validation, and integrating multi-omics with imaging to develop early detection biomarkers and target cross-system interactions for intervention.

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Disclosure

The relevant work carried out by this institute is an in-depth exploration based on the previous achievements of this research group. Throughout the research process, the research subjects involved are the same group of cases. The purpose is to further analyze the imaging data of this group of cases and use more advanced technical means to fully explore the scientific information contained therein, deepen the understanding and understanding of related issues, thereby expanding and improving the previous achievements and contributing more valuable research findings to the academic development of this field.

The authors report no conflicts of interest in this work.

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