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Gender differences in major depressive disorder at different ages: a REST-meta-MDD project-based study

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Abstract

Background Major depressive disorder (MDD) is a highly heterogeneous disease, with differences in clinical manifestations among depression patients based on onset ages and genders. The neural mechanisms underlying these differences remain unclear. In this study, we utilized resting state functional imaging data from a large sample database and adopted the ReHo method to investigate gender differences in local brain function in MDD patients across different onset age groups.

Methods The study included 364 MDD patients and 695 healthy participants who were part of the REST-meta-MDD project. Regional homogeneity (ReHo) assessed gender disparities in MDD and healthy individuals within groups delineated by gender and onset age (young group: 18–29 years; middle-aged group: 30–45 years).

Results Among the young MDD groups, there were significant gender differences in the right superior frontal gyrus, right inferior frontal gyrus, left superior temporal gyrus, and right superior parietal lobule, with male MDD patients having higher ReHo values compared to females. When compared to healthy males, male MDD patients exhibited elevated ReHo values in the right superior parietal lobule. In the middle-aged groups, a marked ReHo difference was observed in the bilateral cerebellum posterior lobe, with female MDD patients showing higher ReHo values.

Conclusions The functional mechanisms of MDD differ between genders and show distinct variations across different onset age groups. These findings underscore the importance of developing personalized interventions that address the unique needs of MDD patients, tailored to their gender and age, and necessitate the development of antidepressant medications targeted at each gender-age subgroup.

Keywords Depressive disorder, Magnetic resonance imaging, functional, Gender, Onset age

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Background

Major depressive disorder (MDD) is a neuropsychiatric disease characterized by core symptoms such as emotional dissonance, depressed mood, guilt, anhedonia, and cognitive and behavioral symptoms [1]. It affects over 300 million people globally [2], with a lifetime prevalence rate exceeding 20% [3].

Depression is a highly heterogeneous condition, with gender differences contributing to its variability.Significant gender disparities exist in MDD's morbidity, symptom presentation, and response to antidepressant treatment. Women exhibit twice the morbidity of singular MDD episodes and four times that of recurrent MDD compared to men [4, 5]. Moreover, female MDD patients tend to experience more severe symptoms and higher subjective distress than their male counterparts [6, 7]. Women are more prone to comorbid anxiety [8], while men are more susceptible to comorbid substance use disorders [9]. Additionally, the onset age significantly contributes to the heterogeneity observed in MDD. Literature suggests variances in heritability, illness severity, and chronicity of MDD symptoms between early-onset MDD (age<30) and late-onset MDD (age>30) [10, 11]. Furthermore, MDD onset in middle-aged patients (age>45) may be influenced more by vascular factors [12]. There are notable differences in MDD across genders and onset ages, presenting challenges in objective diagnosis and precise treatment of the disorder.

Resting State fMRI (rs-fMRI) is a prevalent technique in the study of mental disorders due to its non-invasive and radiation-free nature.Rs-fMRI does not necessitate any specific tasks or external stimuli, facilitating easier cooperation from patients. This method is crucial in researching the pathological mechanisms underlying emotional and cognitive disorders. Recent studies using rs-fMRI have highlighted gender disparities in regional cerebral activity and brain structure in MDD. Tu et al. [13] employed ReHo and the ALFF method to investigate gender differences in MDD, determining that the occipital lobe, calcarine, dorsolateral prefrontal cortex (DLPFC), median cingulate and paracingulate gyri (DCG) are pivotal in explaining these differences. In MDD females compared to males, the ALFF values decreased in the right superior occipital gyrus, while the ReHo values in the left calcarine and left dorsolateral superior frontal gyrus diminished. In a separate study, Sun et al. [14] used the ReHo method to discern gender differences in brain activity among recurrent depression (RDE) patients. They identified significant disparities in the right middle temporal gyrus, right thalamus, and left posterior cerebellar lobe. Furthermore, interactions between gender and depression diagnosis were evident in the left middle frontal gyrus, left precentral gyrus, and right insula.

Numerous studies have investigated the mechanisms underlying gender differences in depression from various angles. However, these studies often report inconsistent brain regions exhibiting gender disparities, which might be attributed to their limited sample sizes (with fewer than 50 patients) and other sources of heterogeneity, such as the onset age of MDD. Shen et al. [15, 16] discovered that, compared to early-onset depression in adults (EOD, 18–29 years old) and late-onset depression in adults (LOD, 30–44 years old), the grey matter volume (GMV) in the right posterior cingulate cortex was reduced in the EOD group. This group also exhibited a significant increase in ReHo in the left precuneus and a decrease in the right fusiform, suggesting varying pathological mechanisms in adult depression patients of different age groups. Previous studies utilized age as a covariate to examine gender disparities in local brain activity associated with MDD. However, these studies failed to independently assess the influence of gender and onset age, compromising the consistency and accuracy of their findings.

In contrast, the present study utilized extensive data samples from MDD patients sourced from the REST-meta-MDD project, mitigating the potential overestimation bias associated with smaller samples [17, 18]. Drawing from prior research, our study selected MDD patients with a course of less than 12 months in the database and divided them into a young group (18–29 years old) and a middle-aged group (30–45 years old) of MDD patients (young group representing early- onset depression, middle-aged group representing late-onset depression), and selected a healthy control (HC) group of corresponding ages. This study used the ReHo method to analyze the differences in MDD patients of different genders at different onset ages, minimizing potential confounding factors such as sample size, onset age, gender, and vascular diseases in older populations. This aids in providing beneficial assistance for the precise identification and treatment of MDD.

Methods

Clinical materials and groups

The study data were from the open, multisite dataset provided by the REST-meta-MDD project (http://rfmri.org/REST-meta-MDD) [19], encompassing 25 datasets from 2,428 individuals (1,300 MDD patients and 1,128 HCs) across 17 hospitals in China. All participants underwent T1-weighted structural MRI and fMRI. Data collection received approval from the respective local ethics committees, ensuring all REST-meta-MDD project data were de-identified and anonymized to maintain participant privacy.To minimize site effects on the results, we applied several techniques and statistical methods. In the data preprocessing phase, we normalized the imaging data

across different sites to ensure uniformity. During statistical analysis, site was included as a covariate to account for any potential site-specific biases. We also evaluated the sample size and data quality from each site to ensure compliance with study standards. These steps were taken to enhance the reliability and accuracy of the results.

Participants were excluded based on the following criteria: (1) overlapping data records; (2) age < 18 or > 45 years; (3) MDD diagnosis with an HDRS score < 17; (4) illness duration exceeding 12 months; (5) incomplete data on gender, years of education, or HDRS for MDD patients; (6) incomplete gender and education information for HC; (7) subpar image quality; or (8) study centers with fewer than 10 participants in any given group.

According to the onset age, Drawing from prior research [15, 16], patients were categorized into two groups: the young group (18–29 years) and the middle-aged group (30–45 years). HCs were similarly segmented by their age during fMRI scanning. Subsequently, the young group consisted of 71 young male MDD, 109 young female MDD, 203 young male HC, and 243 young female HC. The middle-aged group was divided into: 49 middle-aged male MDD, 135 middle-aged female MDD, 108 middle-aged male HC, and 141 middle-aged female HC.

Data preprocessing and definition

R-fMRI data were preprocessed at each site using the same DPARSF protocol [20] (Supplementary material) and ReHo values were calculated. ReHo, defined as the rank-based Kendall Consistency Coefficient (KCC), assessed the synchronization among adjacent voxel time patterns (27 voxels).

Statistical analysis

Demographic data were analyzed using SPSS 26.0. Continuous data were represented as means ± standard deviations (SD). One-way ANOVA compared the age and education distribution across the four youth and middle-aged patient groups. A two-factor ANOVA, considering gender (male and female) and diagnosis (MDD and HC), contrasted the demographic parameters. Comparison of the illness duration and HDRS scorese between two patient groups use two sample t-tests.Significance was ascertained at $p < 0.05$.

The SPM 12 two-way ANOVA, focusing on the youth and middle-aged groups, integrated gender and diagnosis as inter-group factors; age and education level functioned as concomitant variables to identify cerebral regions with ReHo discrepancies. Resultant values underwent Gaussian random field (GRF) correction using Data Processing and Analysis for Brain Imaging (DPABI) software, establishing statistical significance at a voxel threshold level $p < 0.001$ and a cluster size $p < 0.05$. ReHo values highlighting gender-related cerebral region differences were extracted and subjected to a *post hoc* test (Bonferroni correction, $p < 0.05$). Spearman analysis examined the correlation between ReHo values and HAMA scores in each MDD group.

Results

Demographic data

Within the young groups, significant disparities in age and education years were evident among male MDD, female MDD, HC males, and HC females. Gender significantly influenced age, yet neither diagnosis nor the interaction between gender and diagnosis significantly impacted age. Diagnosis significantly affected education years, whereas gender and its interaction with diagnosis did not. HDRS scores and illness duration were not statistically significant differences between the young male MDD group and the young female MDD group (Table 1).

In the middle-aged groups, age and education years varied significantly among male MDD, female MDD, HC males, and HC females. The interaction between gender and diagnosis significantly influenced age, but neither gender nor diagnosis alone did. Diagnosis significantly impacted education years, while gender and its interaction with diagnosis did not. HDRS scores and illness duration between middle-aged male and middle-aged female MDD patients showed no significant differences (Table 2).

ReHo values in all MDD and HCs

Pronounced differences in ReHo appeared in bilateral regions such as the superior parietal lobules, posterior

Table 1 Demographic and clinical characteristics of the young group

Variables	Young MDD patients		Young HCs		t/F	*p* Value
	Male (*n* = 71)	Female (*n* = 109)	Male (*n* = 203)	Female (*n* = 243)		
Age (years)	24.41 ± 3.49	23.80 ± 3.41	24.19 ± 3.05	23.21 ± 2.77	4.971[a]	0.002[a]
Education years (years)	14.19 ± 3.07	13.71 ± 2.81	15.11 ± 2.29	15.22 ± 1.96	12.810[a]	0.000[a]
HDRS scores (points)	22.73 ± 4.43	22.83 ± 4.50	-	-	0.014[b]	0.950[b]
Illness duration (months)	4.97 ± 3.72	5.16 ± 4.05	-	-	1.659[b]	0.199[b]

MDD = major depressive disorder; HC = healthy control, HDRS, Hamilton Depression Rating Scale 17-item version. [a], two-way ANOVA; [b], two-sample t-test

Table 2 Characteristics of the middle-aged group

Variables	Middle-aged MDD patients		Middle-aged HCs		t/F	*p* Value
	Male (*n* = 49)	Female (*n* = 135)	Male (*n* = 108)	Female (*n* = 141)		
Age (years)	37.43 ± 5.01	36.50 ± 4.39	35.60 ± 4.99	37.55 ± 4.98	3.98[a]	0.008[a]
Education years (years)	12.84 ± 3.27	11.96 ± 3.59	13.66 ± 3.33	13.08 ± 3.81	4.87[a]	0.002[a]
HDRS scores (points)	23.96 ± 5.26	24.17 ± 5.07	-	-	0.115[b]	0.735[b]
Illness duration (months)	5.91 ± 3.81	5.49 ± 3.97	-	-	0.186[b]	0.667[b]

MDD = major depressive disorder; HC = healthy control, HDRS, Hamilton Depression Rating Scale 17-item version. [a], two-way ANOVA; [b], two-sample t-test

Table 3 Differential cerebral regions in ReHo values for groups of young group

Cerebral regions	Cluster size (voxels)	MNI coordinates of the peak value			F-value
		X	Y	Z	
Main effcet of diagnosis					
A Right cerebellum posterior lobe	182	39	-60	-54	27.166
B Left cerebellum posterior lobe	202	-21	-33	-57	27.058
Main effcet of gender					
A Right superior frontal gyrus	52	39	60	-9	20.055
B Right inferior frontal gyrus	50	54	24	-9	31.672
C Left superior temporal gyrus	25	-30	9	-39	21.242
D Right superior parietal lobule	22	9	-60	72	20.952

MNI: Montreal Neurological Institute; MNI coordinates are coordinates of peak value, x, y, and z represent coordinates of peak values in differential cerebral regions in MNI coordinates; GRF correction, threshold voxel level $p < 0.001$, cluster size $p < 0.05$.

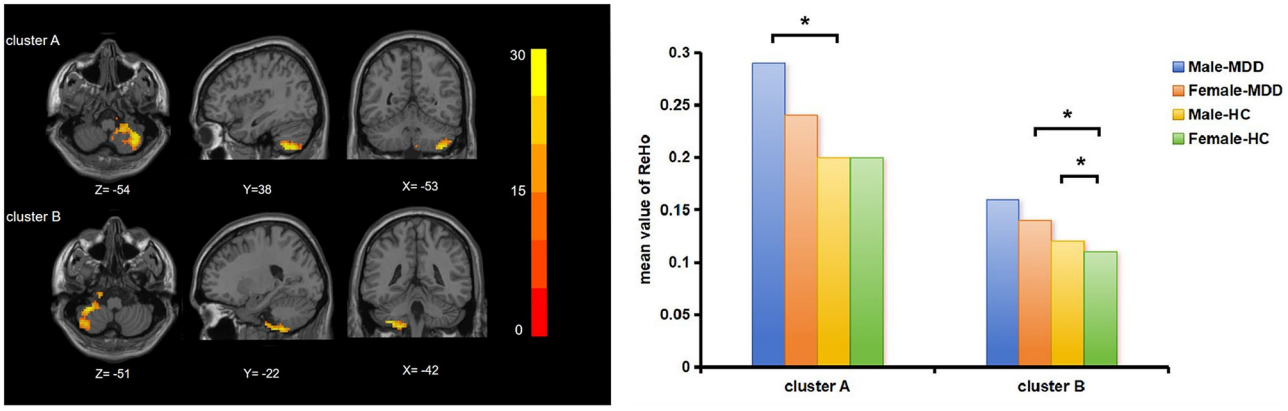

Fig. 1 Statistical maps showing main effects of diagnosis in ReHo among the four young groups (GRF correction, $p < 0.05$). Regions included (A) Right superior frontal gyrus; (B) Left cerebellum posterior lobe.The graph shows the ReHo values extracted from regions with the main effect of diagnosis group.*Represents a significant difference detected ($p < 0.05$)

central gyrus, lateral occipital, anterior cuneiform lobe, lingual gyrus, temporal lobe, and cerebellar regions(SI).

ReHo values in young groups

In terms of diagnosis's main effects, ReHo differences were evident among the young groups in the left and right cerebellum posterior lobe (GRF correction, $p < 0.05$). Young male MDD patients had elevated ReHo values in the right cerebellum posterior lobe compared to young male HCs. Both young male HCs and female MDD demonstrated significantly higher ReHo values in the left cerebellum posterior lobe than young female HCs (Bonferroni correction, $p < 0.05$) (Table 3; Fig. 1).

Regarding gender's main effects, significant ReHo differences existed among the young groups in the right superior frontal gyrus, right inferior frontal gyrus, left superior temporal gyrus and right superior parietal lobule (GRF correction, $p < 0.05$). Young male MDD patients exhibited increased ReHo values in these regions compared to young female MDD patients (Bonferroni correction, $p < 0.05$). The young male MDD also showed a heightened ReHo value in the right superior parietal lobe when contrasted with young male HCs. Young male HCs displayed a higher ReHo in the right superior frontal gyrus and right inferior frontal gyrus than young female HCs (Bonferroni correction, $p < 0.05$) (Table 3; Fig. 2).

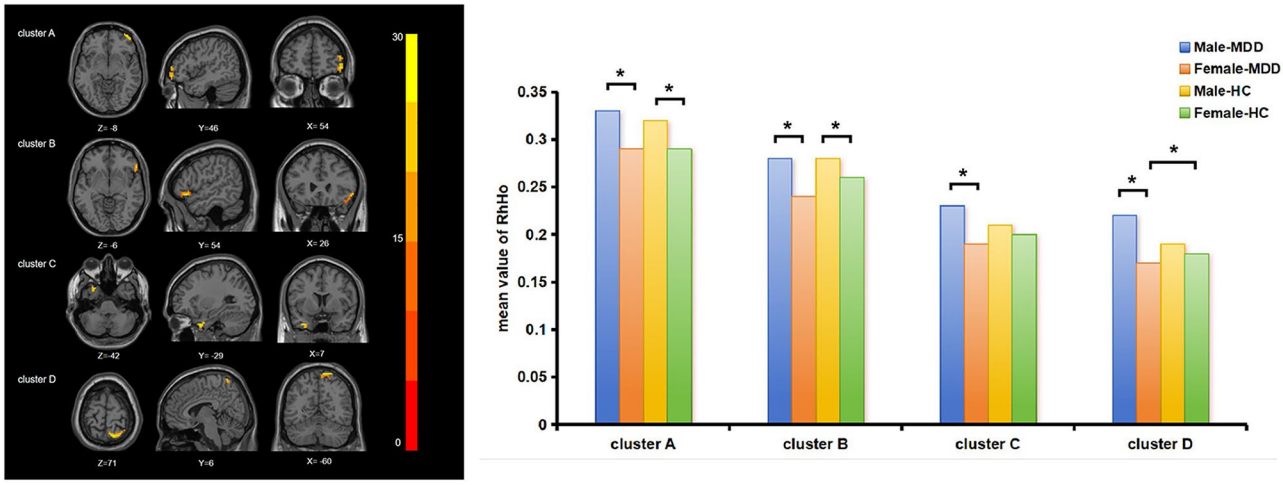

Fig. 2 Statistical maps showing main effects of gender in ReHo among the four young groups (GRF correction, $p<0.05$). Regions included (A) Right superior frontal gyrus; (B) Right inferior frontal gyrus; (C)Left superior temporal gyrus; (D) Right superior parietal lobule. The graph shows the ReHo values extracted from regions with the main effect of gender group.*Represents a significant difference detected ($p<0.05$)

Table 4 Differential cerebral regions in ReHo values for groups of middle-aged group

Cerebral regions	Cluster size (voxels)	MNI coordinates of the peak value			F-value
		X	Y	Z	
Main effcet of diagnosis					
A Left anterior cuneiform lobe	5116	36	-30	57	32.961
Bilateral cerebellum					
Bilateral posterior central gyrus					
B Right superior temporal gyrus	629	45	-51	27	27.693
Right insula lobe					
Right frontal orbital cortex					
Main effcet of gender					
Bilateral cerebellum posterior lobe	495	18	-48	-51	24.127

MNI: Montreal Neurological Institute; MNI coordinates are coordinates of peak value, x, y, and z represent coordinates of peak values in differential cerebral regions in MNI coordinates; GRF correction, threshold voxel level $p<0.001$, cluster size $p<0.05$.

Regarding the main effects of the gender-by-diagnosis interaction, no significant ReHo differences were observed among the four groups. Furthermore, no correlations were observed between ReHo values and HDRS scores in each differential cerebral region for MDD.

ReHo values in middle-aged groups

In terms of diagnosis's main effects, significant ReHo disparities were found among the middle-aged groups in the bilateral posterior central gyrus, the bilateral lingual gyrus, the left anterior cuneiform lobe, the right superior temporal gyrus, the right insula lobe, the rihgt frontal orbital cortex and the bilateral cerebellum (GRF correction, $p<0.05$). In these regions, the ReHo values for middle-aged MDD patients were notably lower than those for middle-aged HCs of the same sex (Bonferroni correction, $p<0.05$). (Table 4; Fig. 3).

Regarding gender's main effects, significant ReHo differences were observed among the four middle-aged groups in the bilateral cerebellum posterior lobe (GRF correction, $p<0.05$). Middle-aged male MDD patients displayed a marked decrease in ReHo values of the bilateral cerebellum posterior lobe compared to their female counterparts (Bonferroni correction,$p<0.05$) (Table 4; Fig. 4).

Considering the main effects of the gender-by-diagnosis interaction, no significant ReHo differences were identified among the four groups. Additionally, there was no correlation between ReHo values and HDRS scores in each differential cerebral region for MDD.

Discussion

This study utilized a comprehensive multi-site sample from the REST-meta-MDD project, and used the ReHo method to discern gender variances in local brain function within different onset aged MDD patients. One possible reason for the observed gender differences across age groups is the varying impact of hormones on brain structure and function during development and adulthood. Hormonal changes, particularly those related to

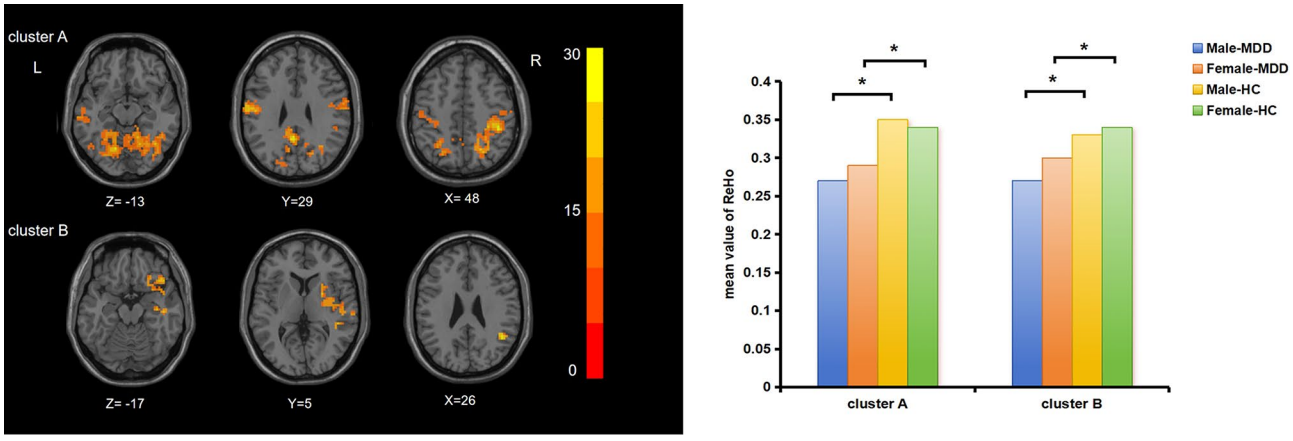

Fig. 3 Statistical maps showing main effects of diagnosis in ReHo among the four middle-aged groups (GRF correction, $p < 0.05$). Regions included (A) Left anterior cuneiform lobe, bilateral cerebellum and bilateral posterior central gyrus; (B)Right superior temporal gyrus, right insula lobe and right frontal orbital cortex. The graph shows the ReHo values extracted from regions with the main effect of diagnosis group.*Represents a significant difference detected ($p < 0.05$)

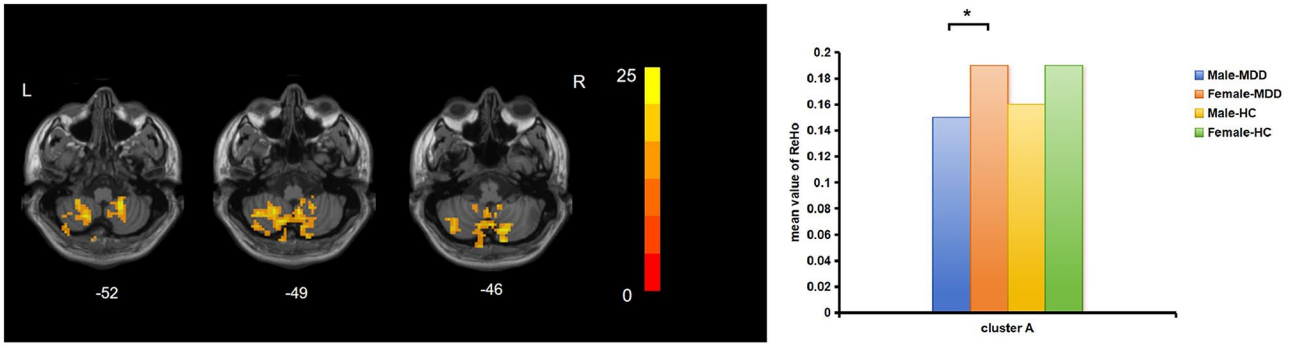

Fig. 4 Statistical maps showing main effects of gender in ReHo among the four middle-aged groups (GRF correction, $p < 0.05$). Regions included bilateral cerebellum posterior lobe. The graph shows the ReHo values extracted from regions with the main effect of gender group.*Represents a significant difference detected ($p < 0.05$)

estrogen and testosterone, are known to influence brain activity and connectivity. This hormonal impact could contribute to the gender-specific ReHo value variations seen in both young and middle-aged MDD patients [21]. Additionally, socio-cultural factors, such as societal roles and stressors, might lead to different neural pathways developing in males and females, further driving gender disparities in brain activity. These variations underscore the importance of considering gender-specific treatment approaches for MDD [22].We ascertained that among young MDD groups, the brain regions with gender differences are the right superior frontal gyrus, right inferior frontal gyrus, left superior temporal gyrus and right superior parietal lobule, the ReHo values of male MDD in these regions are significantly exceeded those in female MDD.In contrast with healthy males, male MDD patients exhibited elevated ReHo values in the right superior parietal lobule. For the middle-aged groups, a pronounced ReHo value discrepancy in the bilateral cerebellum posterior lobe existed between male and female MDD patients, with females presenting higher values. Our findings robustly indicate that MDD's functional mechanisms diverge between genders. Moreover, the functional intricacies of gender differences in MDD also fluctuate across age brackets. This research elucidates novel perspectives on the neuropathological mechanisms driving gender discrepancies in MDD.

In this study, discernible gender-related differences in brain activity were identified among young MDD patients. Notably, distinct activity patterns emerged in the right superior frontal gyrus, right inferior frontal gyrus, left superior temporal gyrus and right superior parietal lobule. Nonetheless, these variations bore no correlation to MDD severity. The temporal lobe, responsible for processing negative emotions and fear, exhibits heightened activity that can impede cognitive function and conflict resolution in adult MDD patients [23, 24]. The lack of correlation between these brain activity variations and MDD severity suggests that gender-based differences may reflect underlying biological processes rather than symptom intensity. The heightened activity in the temporal lobe could be attributed to its role

in emotion processing, which might be influenced by gender-specific factors such as socialization patterns and coping mechanisms. Given that MDD is a multifaceted disorder, these gender-based discrepancies may represent different paths of disease progression or coping strategies, indicating that gender might play a role in how MDD manifests at the neural level. Both genders demonstrate enhanced activation in the left temporal lobe during the object recognition phase of vocabulary extraction, underlining gender disparities in temporal lobe-mediated situational language memory [25]. Certain studies posit gender-based volume variations in the left temporal lobe among the youth, potentially providing the structural foundation for distinct cognitive functions [26]. The frontal orbital cortex, vital for diverse cognitive and emotional tasks, has associations with MDD [27–29]. A dysfunction in the prefrontal region of the frontoparietal network augments MDD and suicide risk [30, 31]. Moreover, glutamate-related gene expression varies between male and female MDD patients [32], with diminished gray matter volume in the prefrontal cortex increasing susceptibility in male MDD patients [33]. Previous research indicates that heightened information complexity amplifies bilateral posterior parietal lobe blood flow [34]. However, for MDD patients, this results in decreased flow [35]. Such parietal cortex impairment can stifle new information absorption and learning [36]. The superior parietal lobule, a pivotal segment of the frontal parietal network, plays a role in attentional cognitive control and emotional regulation [36, 37]. Ultimately, the observed gender-specific brain activity variances might align more with MDD-related youth suicide incidence and risk than with symptom severity.

For middle-aged MDD patients, ReHo showcases gender differences. Contrary to the young MDD cohort, middle-aged participants exhibited ReHo value variations in distinct cerebral regions, especially the bilateral cerebellum posterior lobe (specifically regions VII, VIII, and Crus II of the posterior cerebellar lobe). Yet, these cerebellar ReHo values held no significant relation with MDD scores. With its role in mood regulation and cognitive function, cerebellar ReHo values might differentiate subclinical from MDD, and refractory from non-refractory depressive disorders [38–40]. The cerebellum's receipt of data from cortical and limbic systems, crucial for emotional regulation, underscores that cerebellar malfunctions might escalate mental strain in patients [41]. Furthermore, diminished 5-hydroxytryptamine receptor binding (5-HTT) in the cerebellar hemisphere correlates with heightened impulsivity in suicide-attempting MDD patients [42]. These observations suggest that the bilateral posterior cerebellar lobe's regional cerebral activity disparities in middle-aged MDD patients might relate to augmented impulsivity and a heightened rate of successful suicide attempts, especially in males. Nonetheless, no correlation emerged between ReHo values and HAMD scores in this study.

The findings indicate that MDD's pathophysiological mechanisms exhibit gender-based differences and onset age-related variations. While regional cerebral activity differences appear in both healthy subjects and MDD patients, specific regions differ. Notably, ReHo values did not denote MDD severity, given the absence of correlation with depression scores. Additionally, compared to male HCs, young male MDD patients exhibit elevated ReHo values in the right superior parietal lobule. This suggests that this region might be pivotal in diagnosing and treating early ontset male MDD. Hence, shifts in ReHo values could offer diagnostic cues for this demographic, warranting further exploration.

Significant gender-related variations in brain activity were observed between healthy males and females. Male youths demonstrated enhanced activity in the right frontal orbital cortex relative to their female counterparts, whereas middle-aged females displayed heightened cerebellar activity. These observations are consistent with prior research on gender disparities in brain structure and function [43–45]. However, the extent to which these differences influence gender disparities in MDD, as documented in previous literature [46], remains inconclusive. The findings suggest that gender-related variations in MDD mirror typical disparities in brain development across genders at different life stages, hinting at a possible connection between gender-related MDD mechanisms and standard brain maturation.

The present study acknowledges certain limitations. The database provided incomplete information regarding patient medication, disease progression, and recurrence. Given that participants were sourced from this database, the analysis was constrained to the available data, thus excluding certain indicators from the study.

Conclusions

This study confirms the presence of gender-specific differences in regional cerebral neurological activity among MDD patients across various age groups. Our findings suggest that gender disparities in MDD-related brain function are influenced by age at onset, with distinct patterns emerging in different age brackets. In young MDD patients, the key regions of gender disparity were the right superior frontal gyrus, right inferior frontal gyrus, left superior temporal gyrus, and right superior parietal lobule. For middle-aged MDD patients, significant gender-based differences were primarily observed in the bilateral cerebellum posterior lobe.These results highlight the need for continued research to uncover the underlying mechanisms driving these gender disparities in cerebral activity. Future studies should aim to explore how

these gender-based differences in brain function influence MDD's clinical presentation, treatment response, and long-term outcomes. A deeper understanding of these differences could inform the development of gender-specific treatment strategies and provide a basis for the development of antidepressant medications targeted at each gender-age subgroup.

Abbreviations

MDD	Major depressive disorder
fmri	Functional magnetic resonance imaging
reho	Regional homogeneity
rs-fmri	Resting State fmri
RDE	Recurrent depression
GMV	Grey matter volume
SD	Standard deviations
GRF	Gaussian random field

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-024-06021-6.

Supplementary Material 1

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Not applicable.

Author contributions
P.L. designed the experiments and revised the manuscript. X.T collected and analyzed the data and wrote the manuscript. L.L., N.H. and L.T. participated in the discussion and offered some good ideas. All authors have read and agreed to the published version of the manuscript.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Data collection received approval from the respective local ethics committees, ensuring all REST-meta-MDD project data were de-identified and anonymized to maintain participant privacy. I confirm that all methods were performed in accordance with the relevant guidelines. All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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