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Cognitive and clinical dimensions of structural and functional insula alterations in patients with depression: a resting-state fMRI study

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ABSTRACT

Aim: Depression is characterized by pervasive cognitive and emotional disturbances, yet the neural mechanisms underlying these deficits remain incompletely understood. **Method:** This study utilized multimodal neuroimaging, including resting-state functional MRI and structural T1-weighted imaging, alongside the MATRICS Consensus Cognitive Battery (MCCB) and the Hamilton Depression Rating Scale (HAMD), to delineate the structural and functional alterations in the insula in first-episode, medication-naïve patients with depression. **Result:** Compared to matched healthy controls, patients with depression exhibited significant reductions in gray matter density in the left insula, which were robustly associated with impairments in reasoning and problem-solving abilities. Mediation analyses revealed that insular gray matter density mediated the relationship between depressive symptom severity and cognitive deficits, emphasizing the insula's critical role in linking emotional and cognitive dysfunctions. Furthermore, functional connectivity analyses identified disrupted insula-medial prefrontal cortex circuits, highlighting their contribution to the pathophysiology of depression. **Conclusion:** These findings underscore the insula's dual role as a structural and functional hub in depression, advancing our understanding of the neural substrates of cognitive dysfunction and informing potential targets for intervention.

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Depression; insula; brain structural abnormalities; Brian functional abnormalities; reasoning and problem-solving

1. Introduction

The insula is a central hub with extensive projections that integrate various sensory and cognitive processes [1]. It plays a pivotal role in the core symptoms of numerous disorders. Notably, the insula is a central node of the salience network, involved in detecting and integrating information as well as filtering interoceptive and emotional cues from the environment [2,3]. Functionally, the insula is particularly associated with psychological pain, empathy, and disgust processing in individuals with depression, as well as the switching between interoceptive and external attention. Consequently, the insula has garnered increasing attention not only in neuroscience but also in psychiatry [2].

Structurally, the insula can be divided into three subregions based on morphological differences: granular (posterior), agranular (anterior), and dysgranular (middle) insula [4,5]. Each subregion has distinct functions. The ventral anterior insula is connected to the anterior cingulate cortex, the dorsal anterior insula is co-activated with the dorsal anterior cingulate cortex, and the posterior insula is linked with primary and secondary somatosensory cortices [6]. Functional neuroanatomical studies indicate that the ventral anterior insula is responsible for affective and chemical sensory processing, the dorsal anterior insula for cognitive and executive control, and the posterior insula for somatosensory and sensorimotor functions [7]. Meta-analyses by Kurth et al. have revealed similar conclusions, demonstrating the insula's role in sensorimotor, socio-emotional, cognitive, and olfactory-gustatory processing [8,9]. Early research has shown the role of the insula and its subregions in different cognitive domains. Although the segregation of subregions somewhat reduces the multimodal integration within subregions [10,11], network analyses emphasize the overlap in connections between subdivisions and the high interconnectedness of the dorsal anterior insula [12,13].

The insula plays a central role in interoception and is significantly implicated in various psychiatric disorders, including depression [14–17], bipolar disorder,

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Table 1. Demographic and HAMD scores of patient and control groups.

	Mean ± SD		
	Healthy Controls ($n = 28$)	Patients ($n = 26$)	t/χ2 (p)
Age	30.12 ± 6.49	26.84 ± 8.58	1.10(.275)
Gender	1.51 ± 0.51	1.69 ± 0.47	2.59(.108)
Education Years	15.24 ± 3.26	15.37 ± 2.69	−0.19(.851)
HAMD	0.82 ± 1.36	22.57 ± 7.21	−20.38(<.001)

and schizophrenia [18,19]. In depression, structural and functional alterations in the insula, including abnormal connectivity and interoceptive dysfunction, contribute to emotional and sensory disturbances [20–23]. Specifically, in terms of function, the insula's involvement in numerous cognitive functions and its prominent role in various diseases reflect its importance and susceptibility to disturbances, leading to functional abnormalities. It is well-known that neural hubs like the insula (so-called cortical 'rich clubs') are vulnerable to various symptoms and external events [24]. From a structural perspective, previous studies have reported reduced insular volume in patients with depression [16,25]. Moreover, a causal structural covariance network analysis suggests that the reduction in gray matter volume originates in the right insula and progressively impacts other brain regions as the duration of the illness increases [26]. However, how and to what extent depression may alter the insula at the structural level remains largely unclear.

Additionally, emotional and cognitive impairments, particularly in self-regulation, lead to biases in memory and attention to negative life events, resulting in abnormal emotional states that affect advanced cognitive functions. In these abnormal mechanisms, the insula plays a critical role [2,27]. Depressed patients show increased weighting of negative information during emotional processing [28]. The insula processes incoming emotional information, enhancing the salience network's response to emotional stimuli, thus increasing sensitivity to negative emotions [2,29]. Some studies have linked core symptom screening with brain function, showing significant correlations between the insula and anhedonia, as well as abnormal emotional pain (psychache) or physical pain [30,31]. Therefore, functional abnormalities in the insula are likely a source of structural abnormalities.

This study aims to explore the relationship between gray matter density, functional connectivity, and cognitive abilities in individuals with depression using a stepwise approach. Initially, we performed a stepwise analysis of gray matter density differences across various brain regions, controlling for potential confounding factors such as education level, gender, and age. Next, we employed mediation analysis to examine the role of the insula in linking depressive symptoms to cognitive functions. Building on this, we conducted moderated mediation analysis to investigate the impact of group differences on the functional connectivity between the insula and the prefrontal cortex. Through these progressively structured analytical steps, we seek to provide a comprehensive perspective on the insula's role in the relationship between depression and cognitive impairment, offering theoretical insights for future research in this field.

2. Methods

2.1. Participants

This study recruited 26 first-episode, medication-naive patients with depression based on DSM-5 criteria from Beijing Huilongguan Hospital, China (9 patients were excluded due to poor quality of structural and functional MRI data or MATRICS Consensus Cognitive Battery (MCCB) [32,33] assessments). The patient and control groups were matched for age and gender, ensuring no significant differences between the groups, and efforts were made to maintain equal sample sizes. Additionally, 28 age- and gender-matched healthy controls were recruited based on DSM-5 criteria (2 controls were excluded due to data quality issues, with the exclusion criterion being mean framewise displacement greater than 0.2).

Inclusion criteria included: Participants aged 18-55 years, of any gender, who were first-visit outpatients meeting the DSM-5 diagnostic criteria for depression, screened using the Mini International Neuropsychiatric Interview (MINI). Patients were required to be experiencing a current depressive episode of moderate or greater severity (17-item Hamilton Depression Rating Scale (HAMD) (34] score >17). They had not taken antidepressants, antipsychotics, sedatives, hypnotics, or any other medications affecting cognitive function for at least two weeks prior to inclusion.

Exclusion criteria included: Participants with comorbid psychiatric disorders according to DSM-5 criteria; depression with psychotic features; comorbid personality disorders or intellectual disability; mixed episodes or rapid cycling; alcohol or substance dependence/abuse within the past year; severe or unstable physical illnesses within the past 12 months; severe suicidal tendencies or recent suicide attempts; inability to complete assessments due to agitation, impulsivity, or non-cooperation; pregnancy, lactation, or plans to conceive during the study period; auditory or visual impairments; and contraindications for MRI scanning.

Healthy controls were matched for age (±5 years), sex, and handedness, with no history of psychiatric disorders or substance abuse/dependence, no current use of CNS-acting drugs, and no history of mood stabilizers, antidepressants, or antipsychotics. They had no alcohol use in the past week and no serious or unstable physical illnesses in the past 12 months.

2.2. Disease assessment and cognitive tests

Cognitive functions were assessed using the MCCB, a standardized tool designed to evaluate seven cognitive domains: processing speed, verbal learning and memory, working memory, reasoning and problem-solving, visual learning and memory, social cognition, and vigilance. The MCCB takes approximately 45 to 60 min to administer in a single session and is typically administered by trained clinicians. This battery is widely used in clinical and research settings to assess cognitive impairment in psychiatric populations, including those with depression.

HAMD were used to assess core symptoms, and demographic variables were also measured for subsequent analyses. The HAMD is a multi-item questionnaire used to screen and evaluate the severity of depression. It was originally published by Max Hamilton in 1960 and revised in 1966, 1967, 1969, and 1980. The questionnaire, designed for adults, assesses depression severity through items on mood, guilt, suicidal ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. It includes 17 items and takes about 20 min to complete.

2.3. Neuroimaging acquisition

We used blood oxygen-dependent resting-state functional MRI (fMRI) and T1-weighted imaging to study brain function, structure, and neurotransmitters. All patients and healthy control participants underwent scanning at the Imaging Department of Beijing Huilongguan Hospital using a Siemens 3.0T high-field MRI scanner (Magnetom Prisma, syngo MRD13D, Erlangen, Germany) equipped with a 64-channel coil. Whole-brain functional neuroimaging was obtained using a T2*-weighted echo-planar imaging (EPI) sequence parallel to the AC-PC line, covering 30 axial slices (each 3.3 mm thick). Repetition time (TR) was 2000 ms, echo time (TE) was 30 ms, flip angle was 90°, voxel size was $3.3 \times 3.3 \times 4\,mm^3$, and field of view (FOV) was $210 \times 210\,mm^2$. High-resolution T1-weighted anatomical images were acquired with a TR of 2300 ms, TE of 3.01 ms, flip angle of 9°, voxel size of $1.0 \times 1.0 \times 1.0\,mm^3$, acquisition matrix of 256×240, and FOV of $256 \times 240\,mm^2$, yielding 176 sagittal slices of 1 mm thickness.

2.4. Neuroimaging preprocessing

T1-weighted images were preprocessed using the FreeSurfer software package (https://surfer.nmr.mgh.harvard.edu/), including DICOM data conversion, hardware calibration, skull stripping, gray and white matter segmentation, cortical reconstruction, and spatial normalization. Quality control and adjustments were performed by imaging technologists and neuroimaging analysts to ensure data accuracy and consistency. Resting-state fMRI preprocessing was performed using the CONN toolbox (https://web.conn-toolbox.org/), including motion estimation, slice-timing correction, fMRI-to-T1w registration, registration to the MNI (Montreal Neurological Institute) standard space, confound estimation, ICA-AROMA, smoothing (FWHM = 6 mm), and regression of confounding factors (including six head motion parameters, as well as white matter and cerebrospinal fluid signals). Subsequent analysis was conducted using preprocessed T1w and fMRI data in standard space.

2.5. Statistical methods

First, appropriate methods (t-tests for age, HAMD scores, and years of education; χ^2 tests for gender) were used to investigate the demographic and HAMD scale differences between the two groups. Second, gray matter density differences between the two groups were compared using two-sample t-tests based on T1-weighted images, with and without HAMD scores as covariates. Particular attention was given to bilateral insula differences. Third, regions showing significant gray matter density differences served as seeds for extracting mean time series within ROIs, constructing first-level GLM models at the individual level, and examining specific brain regions differing in connectivity at the second level. To avoid potential false positives in imaging analyses, family-wise error (FWE) correction based on Monte Carlo simulations with AFNI 3dClustSim was applied, using a height threshold of $p < 0.005$ and an extent threshold of $p < 0.05$. Insula regions were selected from the AAL template, and other regions from meta-analysis-based Neurosynth templates (www.neurosynth.org).

2.6. Mediation analysis

To explore the brain structural and functional characteristics with symptom prediction in advanced cognitive processes, we examined the mediation effect of the

insula and its functional connectivity circuits. Specifically, the HAMD score was treated as the independent variable (X), structural or functional characteristics of insula as the mediator (M), and reasoning/problem-solving ability as the dependent variable (Y). The mediation model was analyzed using bootstrap resampling (5,000 samples) to estimate the significance of direct and indirect effects. The significance of mediation effects was assessed using 5000 bootstrap samples, with 95% confidence intervals not containing zero considered significant.

2.7. Moderated mediation analysis

A moderated mediation analysis was conducted to explore whether the relationship between depressive symptoms, insula gray matter density, and IFG-insula connectivity is influenced by group differences (depressed patients vs. controls). The analysis aimed to determine whether the mediating role of insula gray matter density varies across groups, reflecting differences in the structural-functional relationships between healthy controls and depressed patients. To test this, we used the depressive symptoms as the independent variable (X), insula gray matter density as the mediator (M), insula connectivity circuit as the dependent variable (Y), and group membership as the moderator (W). Conditional indirect effects were examined by testing interaction terms (X×W and M×W) to determine if the strength or direction of these pathways varied across groups. Bootstrap resampling (5,000 samples) was employed to assess the significance of these effects, ensuring robust estimation.

3. Results

3.1. Inter-group differences in demographics and symptoms

First, basic characteristics of the patient and control groups were examined. The results indicated no significant differences in education level ($t = -0.19$, $p = 0.85$), gender ($\chi 2 = 2.59$, $p = 0.11$), or age ($t = 1.10$, $p = 0.28$). Further, to ensure consistent symptom measurement across groups and avoid the influence of cognitive impairment on self-assessment, symptom assessments were conducted by clinicians. Results showed significant differences in depression ($t = 20.38$, $p < 0.001$) and anxiety ($t = -25.54$, $p < 0.001$), with higher scores in the patient group (please see Table 1).

3.2 Gray matter density differences between groups

Next, after controlling for education years, gender, age, and total brain volume, significant gray matter density differences between the depressed and control groups were revealed (see Table 2 and Figure 1). Adding HAMD scores as covariates in the t-tests showed significant differences related to HAMD scores, particularly in the left insula ($t = 3.16$, $p = 0.003$).

3.3. Correlation between insula gray matter density and cognitive functions

We further examined the impact of depression on the left and right insula in relation to advanced cognitive functions. Initially, without grouping, we explored the relationship between HAMD scores, left gray matter density, and advanced cognitive functions. In the ungrouped analysis, a significant correlation was found between HAMD scores and social functioning ($r = -0.31$, $p = 0.02$), as well as between HAMD scores and reasoning and problem-solving abilities ($r = -0.28$, $p = 0.04$).

Furthermore, we revealed a significant relationship between left insula gray matter density and reasoning and problem-solving abilities ($r = 0.39$, $p = 0.004$), which remained significant after controlling for gender, age, and education level ($r = 0.41$, $p = 0.003$).

Table 2. Brain regions with significant gray matter density differences between groups.

Brain Region	Hemis--phere	Cluster Size	t	MNI Coordinate X, Y, Z		
Superior Temporal Gyrus	R	821	5.12	52.5	−22.5	1.5
Middle Temporal Gyrus	R	821	3.90	63	−7.5	−12
Middle Temporal Gyrus	L	153	4.69	−54	−25.5	−13.5
Inferior Frontal Gyrus (p. Triangularis)	R	537	4.69	52.5	43.5	4.5
Inferior Frontal Gyrus (p. Orbitalis)	R	537	3.40	51	31.5	−13.5
Posterior-Medial Frontal	L	102	4.55	−7.5	−15	67.5
Inferior Frontal Gyrus (p. Orbitalis)	R	367	4.25	37.5	28.5	−10.5
Superior Frontal Gyrus	L	60	4.18	−19.5	46.5	34.5
Insula	L	88	3.96	−25.5	22.5	−3
Posterior-Medial Frontal	L	124	3.91	3	16.5	55.5
Putamen	R	59	3.67	27	0	−4.5
Middle Frontal Gyrus	R	91	3.58	39	54	10.5

Notes: FWE correction using AFNI 3dClustSim, with height threshold $p < 0.005$ and extent threshold $p < 0.05$.

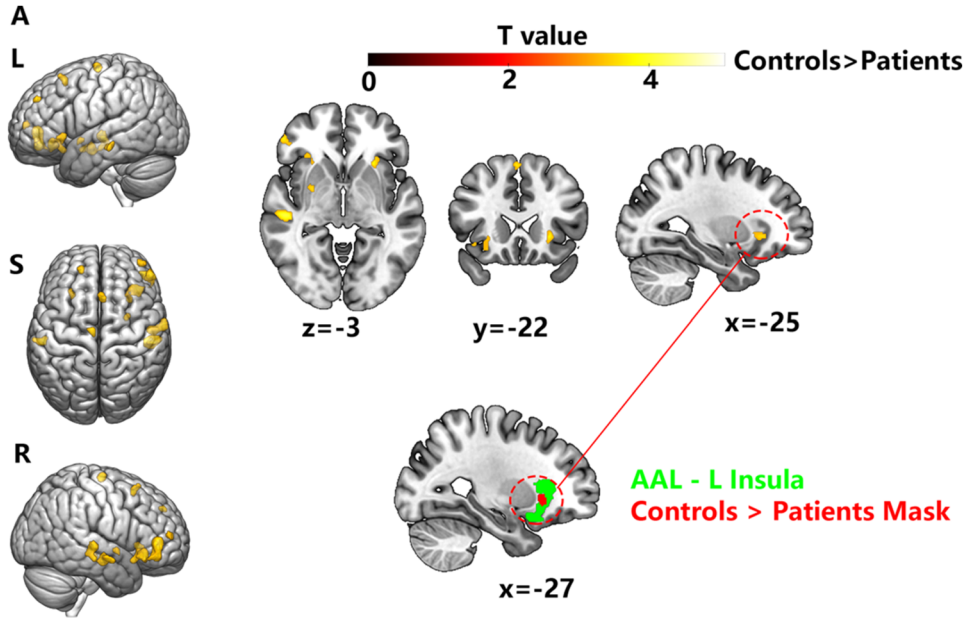


Figure 1. Abnormal gray matter density regions in patients with depression.

Table 3. Brain regions with significant functional connectivity related to HAMD.

Brain Region	Left/Right	Cluster	t	MNI Coordinate X, Y, Z		
Dorsal Medial Prefrontal Cortex	L	42	3.18	−12	56	2

Notes: FWE correction using AFNI 3dClustSim, with height threshold $p < 0.001$ and extent threshold $p < 0.05$.

3.4. Mediation analysis of left insula in predicting cognitive abilities

Subsequent mediation models explored the insula's role in predicting higher cognitive functions based on symptoms. Results showed that the left insula completely mediated the relationship between symptoms and reasoning/problem-solving ability ($F = 5.28$, $p = 0.008$, direct effect 95% bootstrap = [-0.26, 0.07], indirect effect 95% bootstrap = [−0.15, −0.01]).

3.5. Moderated mediation analysis of group differences

Moderated mediation analysis further examined the moderating role of group differences in the mediation process. Results indicated significant moderated mediation effects ($F = 5.3$, $p = 0.008$), but not for the right insula (HAMD→right insula: $F = 3.64$, $p = 0.06$, mediation not established).

The moderating effect of group differences on the relationship between HAMD and left insula gray matter density was significant (HAMD→insula: β = 0.05, 95% bootstrap = [0.01, 0.83]; insula→reasoning ability: β = 45.78, 95% bootstrap = [7.69, 83.88]). The direct effect of the model was not significant (β = −0.09, 95% bootstrap = [−0.26, 0.07]), while the indirect effect was significant (control: β = 1.11, 95% bootstrap = [0.08, 2.77]; depressed patients: β = −0.02, 95% bootstrap = [−0.16, 0.14]). The moderating effect of group differences was significant (index = −1.12, 95% bootstrap = [−2.79, −0.08]).

3.6. Functional connectivity analysis of the insula and cognitive abilities

Further analysis used the left insula as a seed to examine the impact of gray matter abnormalities on functional circuits and higher cognition. Multiple regression analysis revealed a significant relationship between HAMD and the medial prefrontal cortex-insula circuit (See Table 3 and Figure 2). Extracted statistical parameter values from this region were used in subsequent functional connectivity analyses.

Independent sample t-tests showed significant group differences in the medial prefrontal cortex-insula circuit related to HAMD ($t = 2.64$, $p = 0.01$). HAMD negatively correlated with mPFC-insula connectivity ($r = -0.42$, $p = 0.002$), and impaired mPFC-insula circuits positively correlated with reasoning/problem-solving ability ($r = 0.26$,

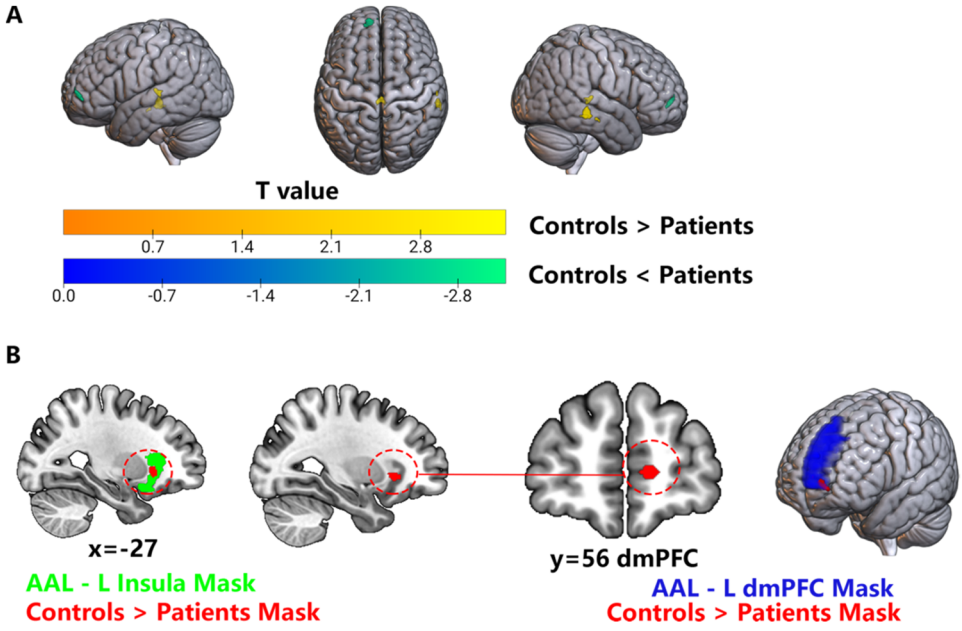


Figure 2. Functional connectivity between the insula and dorsomedial prefrontal cortex associated with HAMD.

Table 4. Brain regions with significant functional connectivity related to reasoning / problem-solving ability.

Brain Region	Left/Right	Cluster Szie	t	MNI Coordinate X, Y, Z		
Inferior Frontal Gyrus (p. Opercularis)	R	276	3.31	54	10	26

Notes: FWE correction using AFNI 3dClustSim, with height threshold $p < 0.005$ and extent threshold $p < 0.05$.

$p = 0.05$), indicating that symptoms affect higher cognition through altered insula circuits.

3.7. IFG-insula circuit abnormalities and their relationship with reasoning/problem-solving abilities

Multiple regression analysis further supported these findings by revealing that the mPFC-insula circuit plays a key role in cognitive abnormalities, although the mediation effect was not established ($F = 2.89$, $p = 0.06$). Further analysis by using multiple regression analysis identified significant neural circuits associated with reasoning/problem-solving ability. Results showed significant prediction by the IFG-insula circuit ($r = 0.42$, $p = 0.001$) (see Table 4 and Figure 3), although unrelated to HAMD.

Further mediation analysis suggested that IFG-insula connectivity abnormalities might relate to gray matter density abnormalities. Left insula gray matter density served as a mediator in the prediction of reasoning/problem-solving ability by HAMD. Results indicated significant mediation effects ($F = 4.53$, $p = 0.02$), with non-significant direct effects ($\beta = 0.16$, $p = 0.50$) and significant indirect effects ($\beta = -0.25$, 95% bootstrap = [-0.44, −0.86]), indicating full mediation.

3.8. Moderated mediation analysis of group differences in the IFG-insula circuit

Moderated mediation analysis showed that group differences significantly moderated the relationship between HAMD and left insula gray matter density (HAMD to insula: $\beta = 0.05$, 95% bootstrap = [0.01, 0.83]; insula to IFG-insula connectivity: $\beta = 159.37$, 95% bootstrap = [51.79, 266.95]). The direct effect was non-significant ($\beta = 0.16$, 95% bootstrap = [−0.30, 0.6]), with significant indirect effects (control: $\beta = 3.86$, 95% bootstrap = [0.47, 9.05]; depressed patients: $\beta = -0.08$, 95% bootstrap = [-0.56, 0.50]). The moderating effect of group differences was significant (index = −3.93, 95% bootstrap = [−9.22, −5.01]).

4. Discussion

This study systematically explored the core role of the insula's function and structure in cognitive abnormalities in depressed patients using MCCB and HAMD

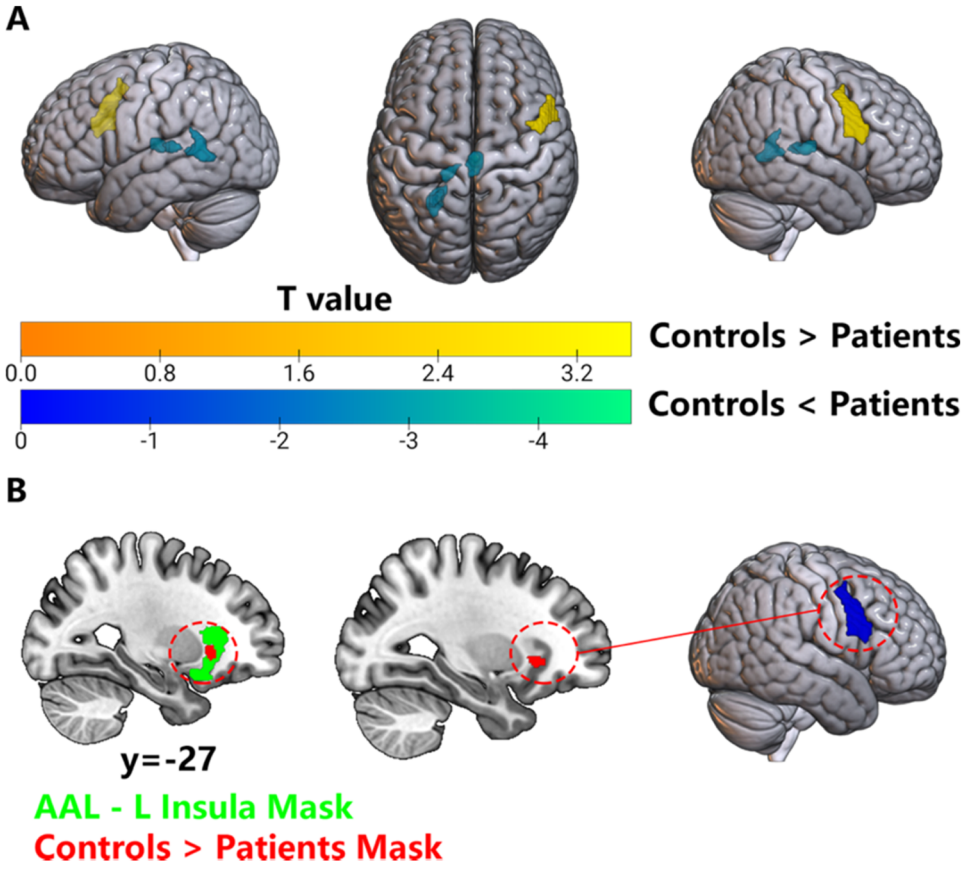


Figure 3. Abnormal IFG-insula functional connectivity related to reasoning and problem-solving.

assessments, along with structural and functional MRI. Preliminary findings revealed the impact of insula structural abnormalities on cognitive function, and the differential effects of structural abnormalities on functional circuits, highlighting the potential importance of the insula in understanding depression.

Previous studies indicate that the insula interfaces between physiological sensation and advanced cognitive systems [27], often implicated in activation and functional circuit abnormalities due to interoception [4], emotional perception, anxiety [35], anticipation [36], and anger, further participating in various cognitive processes. This indicates that the insula, as a central integrative region, could be susceptible to environmental influences impacting cognition in depression. Using HAMD to describe symptoms, this study found significant group differences in insula gray matter density based on HAMD scores, indicating a possible association between higher HAMD scores and decreased insula gray matter density. This aligns with previous literature on stress-related emotional disorders (PTSD [37]; depression [38]; anxiety disorders [39]; conduct disorders and related issues [40]).

Research on insula structural changes and advanced cognition often links it to sensory perception [41], motor functions, visual memory, and executive functions [42], mostly inferred from cognitive performance in patients with organic lesions. The insula's structural abnormalities are also associated with language disorders [43], but studies on memory, reasoning, and problem-solving are scarce. This study revealed potential relationships between insula structural abnormalities and reasoning/problem-solving deficits, suggesting a possible mediating role of depressive symptoms. Previous research has shown abnormal emotional reasoning in depressed patients, as well as deficits in problem-solving, theory of mind [44,45], empathy, and compassion, often considered independent of intelligence. Emotional reasoning, as part of emotional intelligence [46], likely plays a crucial role in core depressive abnormalities. Although previous literature has not directly linked emotional reasoning ability and major depressive symptoms, we hypothesize that the insula mediates the relationship between emotional reasoning abnormalities and symptoms [47], as evidenced by the full mediation effect observed in this study.

In addition to directly bridging symptoms and advanced cognition, insula gray matter density affects functional circuits, leading to functional connectivity abnormalities. Using the left insula as a seed, we found significant negative correlations between HAMD and

medial prefrontal cortex-insula connectivity, suggesting that symptoms lead to reduced functional connectivity, further impairing reasoning/problem-solving ability. Although this study used correlation to demonstrate this conclusion without mediation models, mPFC-insula connectivity is a key node in the interaction between default and salience networks [2,48]. In depression, mPFC connectivity abnormalities are often associated with emotional regulation deficits, manifesting as reduced top-down regulation of emotional responses and regulation by mPFC, resulting in lower functional connectivity in mPFC-insula circuits in depressed patients [49]. Additionally, mPFC participates in memory consolidation and memory-based reasoning, playing an important role in various social and reasoning contexts [50,51]. Therefore, we consider mPFC-insula connectivity may serve as a key functional circuit potentially linking symptoms and higher cognitive deficits.

The predictive value of mPFC-insula connectivity for reasoning/problem-solving ability was relatively weak, prompting further exploration of neural circuits associated with these cognitive functions. Results indicated that IFG-insula connectivity might better predicted reasoning/problem-solving ability, although unrelated to HAMD. Further analysis revealed significant mediation effects, with insula gray matter density influencing IFG-insula connectivity and subsequently impacting reasoning/problem-solving ability, highlighting insula gray matter density and IFG-insula connectivity as important phenotypic markers that warrant further investigation. Given the multifunctionality of the insula, its impact on higher cognition may be indirectly mediated through structural and functional influences, resulting in cognitive abnormalities.

5. Limitations

This study has several limitations. Given the challenges in recruiting first-episode depressed patients, the small sample size in this study may limit its statistical power. Future research should include a larger number of participants to better validate the findings. Secondly, cognitive function and MRI assessments in this study were conducted offline, not using task-based activation or psychophysiological interaction analysis. Spontaneous neural activity during resting or sleep states may aid in memory consolidation, impacting reasoning and memory predictions. Finally, depression with significant gender differences may exhibit cognitive impairments influenced by gender. Although gender differences were statistically controlled, this study did not specifically report gender-related effects on symptoms and cognition, limiting its generalizability.

Author contributions

F. Yan and S. Zan designed the experiments, conducted the imaging data collection and data analysis, and participated in manuscript writing. J. Xu and S. Zhao were responsible for data analysis and manuscript writing. Z. Wang and F. Yang provided guidance for the manuscript writing and final proofreading.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Institutional review board statement

The study was approved by the ethics committee of Beijing Huilongguan Hospital Ethics Committee.

Informed consent statement

All the subjects provided informed consent through an electronic information group.

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Data availability statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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