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Exploring the interaction effects of subclinical hypothyroidism and major depressive disorder on brain networks

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Abstract

Background Major depressive disorder (MDD) often presents alongside physical illnesses, such as a high incidence of subclinical hypothyroidism (SHypo) in patients, highlighting the common occurrence of these comorbidities. Recent research has indicated that the presence of comorbid SHypo in individuals diagnosed with MDD may result in notable alterations in both brain structure and function. This study aimed was to investigate the neurological mechanisms underlying this co-occurrence using a data-driven approach to analyze brain activity patterns.

Methods Twenty-nine patients diagnosed with MDD without any comorbid conditions (nSHypo-MDD) were included in the study, along with 29 MDD patients who also had SHypo (SHypo-MDD), 26 patients with SHypo only, and 29 healthy individuals as controls (HCs). Each participant received resting-state functional magnetic resonance imaging scans and underwent neuropsychological evaluations.

Results We found significantly altered functional connectivity (FC) within the resting-state networks (RSNs) of the ventral and dorsal sensorimotor network (VSMN and DSMN) and occipital pole visual network (PVN) ($p < 0.05$, FDR corrected). A vital interaction effect between SHypo and MDD was detected in the PVN, showing that SHypo-MDD patients had higher FC values in the left cuneus than nSHypo-MDD patients. Serum-free triiodothyronine (FT3) levels in SHypo-MDD patients demonstrated an inverse relationship with FC values of the right supplementary motor area (SMA.R) ($r = -0.563$, $p = 0.003$). Furthermore, the FC values in the left cuneus are positively associated with the Digit Symbol Substitution Test (DSST) scores ($r = 0.507$, $p = 0.008$).

Conclusions Our study reveals significant FC changes in SHypo-MDD patients, particularly in the PVN, VSMN, and DSMN, suggesting compensatory mechanisms that mitigate cognitive deficits and highlighting the need for integrated management of SHypo and MDD to improve cognitive outcomes.

Keywords Brain Networks, Subclinical Hypothyroidism, Major depressive disorder

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Background

Depression, a leading cause of disability worldwide, affects over 332 million individuals and significantly impairs quality of life and daily functioning [10]. Major depressive disorder (MDD) is a disorder marked by episodes of profound sadness, cognitive slowing, and decreased ability to engage in physical activities. MDD patients often report physical problems and sometimes coexist with medical conditions [8]. It is estimated that MDD alone, or combined with chronic somatic diseases, represents a significant disease burden around the world [23, 24]. MDD frequently accompanies a range of physical conditions, including heart disease, cancer, persistent pain, and thyroid issues. Recent studies, including ours, have identified a high comorbidity rate between MDD and subclinical hypothyroidism (SHypo), which warrants our attention.

SHypo is recognized by increased serum thyroid-stimulating hormone (TSH) levels alongside normal free thyroxine (FT4) levels [26]. Although frequently asymptomatic, SHypo is linked to several adverse health effects, including cardiovascular disease, abnormal lipid levels, cognitive decline, and diminished quality of life [4, 38]. Likewise, SHypo has been associated with cognitive difficulties, such as impairments in attention, memory, and executive functioning, caused by the influence of thyroid hormones (THs) on the brain through glial cells, impacting neuronal growth, movement, and development [37]. Yin et al. found that individuals with SHypo had notably slower response times and lower task accuracy, suggesting a decline in attentional abilities [46]. A previous task-based fMRI study by Zhu et al. observed decreased activation in the bilateral dorsolateral prefrontal cortex (DLPFC) during n-back tasks, indicating that individuals with SHypo show compromised executive functioning (EF) [54]. Our recent study employing voxel-based morphometry (VBM) demonstrated a significant correlation between alterations in gray matter volume (GMV) and cognitive dysfunction in individuals with MDD comorbid with SHypo, underscoring the significance of neuroimaging in elucidating the neural mechanisms underlying comorbid conditions (Shuai [50, 52]).

Resting-state functional magnetic resonance imaging (rs-fMRI) is a non-invasive method for studying the brain's spontaneous activity while at rest using fMRI technology [31]. Past studies utilizing rs-fMRI have found that people with SHypo may exhibit difficulties in attention regulation and decreased connectivity in the brain circuitry connecting the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) [46]. Our previous study using the regional homogeneity (ReHo) technique found a link between SHypo in MDD and increased ReHo values in specific brain regions (S. [50, 52]).

However, traditional analysis methods often focus on predefined regions of interest or whole-brain analyses that may not capture the complexity of brain network alterations. Independent component analysis (ICA) is a robust data-driven method for blind source separation, which operates without needing any prior assumptions about seed regions [35]. A prior study found that changes in the inherent resting-state functional connectivity (FC) in the sensorimotor network (SMN) and the right anterior network (RAN) may be associated with slight impairments in motor abilities, working memory, focus, and executive functions in people with SHypo [19]. This raises the critical question of whether comorbid SHypo significantly impacts the FC within brain networks. As far as we know, there have been no studies examining this in patients with MDD who also have SHypo. Therefore, exploring the co-occurrence of the two disorders from a network-level view could significantly enhance the current neural frameworks concerning patients with multiple conditions.

Using the rs-ICA technique, this research investigated the neurological foundation for the simultaneous presence of SHypo and MDD. We examined the distinct and combined effects of SHypo and MDD on the FC in four diverse categories of individuals, specifically individuals with MDD who have SHypo or do not have SHypo (SHypo-MDD or nSHypo-MDD) and individuals without MDD who have SHypo or are healthy controls (SHypo or HCs). Next, we investigated the connection between affected brain areas and clinical and cognitive factors within each group. We hypothesize that SHypo-MDD patients may demonstrate FC alterations, impairing their cognitive abilities.

Methods

The study included 29 patients with MDD but no other health conditions (nSHypo-MDD group), as well as 29 patients with MDD who also had SHypo (SHypo-MDD group), enlisted from the Department of Psychiatry at the Affiliated Nanjing Brain Hospital of Nanjing Medical University between July 2019 and February 2021. Twenty-six SHypo patients were enrolled in the Department of Endocrinology at Nanjing First Hospital. The control group consisted of 29 enrolled healthy controls (HCs group). All patients diagnosed with MDD met the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Association., 2013). Participants diagnosed with MDD were mandated to attain a minimum score of 18 on the 17-item Hamilton Depression Rating Scale (HDRS). Subjects were required to meet specific criteria, including being between 18 and 60 years old, right-handed, of Han Chinese descent, and having at least 8 years of education.

The exclusion criteria encompassed individuals with comorbid mental disorders, neurological symptoms or conditions, recent substance abuse or dependence, pregnancy or breastfeeding, significant physical illness history, or contraindications to MRI.

The research protocol received approval from the Ethics Committee of the Affiliated Nanjing Brain Hospital at Nanjing Medical University in adherence to the principles outlined in the Declaration of Helsinki. All participants provided written informed consent.

Clinical assessments

The participants filled out a self-administered health survey that included questions on socioeconomic and demographic factors and their self-reported health status and lifestyle habits. As part of the psychiatric history checklist, critical items like age of onset, number of episodes, and number of hospitalizations will be recorded. The HDRS-17 was used to assess the severity of depressive symptoms. The Hamilton Anxiety Scale (HAMA) was used to assess the severity of anxiety. Experienced psychiatrists conducted all the assessments.

Neurocognitive assessment

All participants underwent a thorough administration of neurocognitive tests. Drawing from previous research, the subtests of these assessments were classified into four main domains: attention, memory, processing speed, and executive function [49, 51, 53]. The Trail Making Test (TMT) A was employed to evaluate attention [29]. Memory function was divided into categories of verbal memory and visual memory. Participants were assessed on their capacity to recall words and images independently using the logical memory (LM) and figural memory (FM) sections of the Wechsler Memory Scale-Revised (WMS-R) [41]. Processing speed was assessed using the Digit Symbol Substitution Test (DSST) [40]. TMT-B evaluated cognitive flexibility to assess executive function, while Digit Span Backward (DSB) tested working memory [42]. These tests were chosen because of their prior use in studies on MDD, demonstrating their practicality [22, 49, 51, 53].

Serum THs level assessments

Fasting venous blood samples from all participants were collected in the early morning. Thyroxine (FT4), triiodothyronine (FT3), and thyroid-stimulating hormone (TSH) levels were assessed through electrochemiluminescence testing with the Roche Company Cobas E601 automated immunoassay. The variability within assays ranged from 3 to 6%, while the variability between assays ranged from 5 to 9%. SHypo was identified by elevated serum TSH levels and normal FT3 and FT4 concentrations. The laboratory reference ranges for TSH were 0.27 to 4.2 mIU/L, while the ranges for FT4 were 12 to 22 pmol/L, and for FT3 were 3.1 to 6.8 pmol/L.

fMRI data acquisition

All participants were scanned with an MRI machine with a magnetic field strength of 3.0 Tesla at the Affiliated Nanjing Brain Hospital of Nanjing Medical University. Foam pads were used to stabilize the head and minimize movement. MRI scans were conducted on the same day as blood sample collection to ensure temporal consistency between physiological and imaging data. Participants were instructed to close their eyes and remain alert during the scan. The anatomic axial and echo-planar imaging parameters matched those from our prior publications (S. [49–53]). Resting-state BOLD-MRI was obtained utilizing conventional functional MRI, employing the gradient-echo and echo-planar imaging techniques. The parameters were set as follows: TR = 3000 ms, TE = 40 ms, FA = 90°, number of slices = 32, FOV = 24 × 24 cm^2, slice thickness = 4 mm, slice gap = 4 mm, matrix size = 64 × 64, in plane voxel resolution = 3.75 mm × 3.75 mm, and 133 volumes.

Data preprocessing and independent component analysis

Data with functionality was analyzed utilizing the software Statistical Parametric Mapping version 12 (SPM12) and RESTplus [16] integrated in the MATLAB toolbox. Each participant's initial ten functional volumes were excluded to achieve scanner equilibration. Additional data preprocessing involved correcting slice timing, addressing head motion, and normalizing spatially. Data points with head movement exceeding 2 mm or 2 degrees were removed from the analysis to prevent any potential impact on the results. Afterward, the regression removed false variances, such as the Friston 24 head motion parameters, cerebrospinal fluid (CSF) signals, white matter (WM) signals, and linear trends. Framewise displacement was computed for every participant based on the model proposed by Jenkinson et al. [15]. Following this, the images underwent spatial normalization to MNI templates. We did not exclude any participants from the fMRI analysis because of excessive head motion. Afterward, the normalized data underwent spatial smoothing with a Gaussian kernel of 6 mm full-width-at-half-maximum.

The fMRI time series underwent ICA analysis with the Group ICA Toolbox (GIFT v4.0c). In our data analysis, we performed four fundamental procedures: reducing dimensionality, conducting group ICA, post-reconstruction, and matching independent and network components. PCA was used to reduce the dimensionality. The Infomax algorithm decomposed all participants' images

into 23 spatially independent components. ICASSO enhanced the stability of independent components (ICs) by running the algorithm 20 times. The GICA algorithm reconstructed spatial maps and time courses for each IC. Network components were chosen based on template matching and visual examination, explicitly mentioning the Yeo template [45].

Statistical analysis

A Multivariate Analysis of Covariance (MANCOVA) was performed to assess the differences in thyroid hormone levels and cognitive functions, while controlling for age and sex. Sex, marital status, and family psychiatric history were compared using a chi-square test. A comparison between HDRS and HAMA scores in SHypo-MDD and nSHypo-MDD patients was conducted using a two-sample *t*-test. A two-way ANOVA was conducted for the neurocognitive tests, controlling for the effects of age and sex. Data analysis was conducted with SPSS 19.0, with statistical significance defined as $p < 0.05$.

Using the reconstructed spatial maps of the participants in each group, we conducted voxel-wise one-sample *t*-tests to analyze functional connectivity within the chosen ICN ($p < 0.05$, FDR corrected). In each group, the masks of the networks were created, and the statistical range for each network was calculated from the combination of the four groups. A two-way ANOVA was conducted using SPM12 to analyze the connectivity within each ICN, with SHypo and MDD as independent variables and age, gender, and years of education as covariates. For every analysis, we utilized a corrected threshold of $p < 0.05$ for the entire brain at the cluster level and a threshold of $p < 0.001$ (uncorrected) for forming clusters. Regions of interest (ROIs) were identified as brain areas showing significant main effects and interactions.

A partial correlation analysis was conducted to examine potential clinical relevance. In this portion, masks were recognized as brain areas that displayed notable variances across the four categories. Changes in FC observed in the masks were associated with THs and cognitive measures while accounting for age, gender, and years of education.

Results

Demographic and cognitive characteristics

Essential demographic and clinical characteristics of nSHypo-MDD, SHypo-MDD, SHypo, and HCs were summarized in Table 1. Significant differences were observed among the four groups in FT4 levels, TSH levels, TMT-A, DSST, and DSB scores ($p < 0.05$). A significant difference in HAMA scores ($p < 0.05$) was observed between the SHypo-MDD and nSHypo-MDD groups, while no significant difference was found in HDRS scores ($p > 0.05$) (see Table 1). The main effects of MDD were observed in attention, processing speed, cognitive flexibility, and working memory, while the main effect of SHypo was found in attention. The interaction was only found in processing speed (see Table 2).

Intranetwork connectivity analysis

Seven independent components (ICs) were identified as the five RSNs among the 23 components. The RSNs produced in Fig. 1 consist of ventral and dorsal sensorimotor network (VSMN and DSMN), occipital pole visual network (PVN), default mode network (DMN), left and right frontoparietal network (LFPN and RFPN), and dorsal attention network (DAN) ($p < 0.05$, FDR corrected).

Significant changes in FC were noted in the PVN, VSMN, and DSMN across the four groups: nSHypo-MDD, SHypo-MDD, SHypo, and HCs (voxel-level $p < 0.001$, cluster-level $p < 0.05$, FDR corrected). Specifically, SHypo demonstrated significant main effects on FC within the VSMN and DSMN (voxel-level $p < 0.001$, cluster-level $p < 0.05$, FDR corrected). Compared to nSHypo-MDD patients, SHypo-MDD patients exhibited increased FC in the left postcentral and the right supplementary motor area (SMA.R) (voxel-level $p < 0.001$, cluster-level $p < 0.05$, FDR corrected).

Furthermore, a significant interaction effect between SHypo and MDD was identified in the PVN, as shown in Fig. 2 and detailed in Table 2. SHypo-MDD patients exhibited significantly increased FC values in the left cuneus compared to nSHypo-MDD patients (voxel-level $p < 0.001$, cluster-level $p < 0.05$, FDR corrected). No significant main effects of MDD were observed in any other comparison (voxel-level $p < 0.001$, cluster-level $p < 0.05$, FDR corrected).

Clinical correlations

Serum FT3 levels in SHypo-MDD patients exhibited an inverse relationship with the FC values of the SMA.R ($r = -0.563$, $p = 0.003$). Moreover, the fractional anisotropy values of the left cuneus showed a positive correlation with the DSST scores ($r = 0.507$, $p = 0.008$) (Fig. 3 and Table 3).

Discussion

This study is among the first to identify distinct FC patterns in SHypo-MDD patients using rs-ICA. The observed increases in FC within the left cuneus and SMA.R highlight specific compensatory neural mechanisms that may distinguish SHypo-MDD from other MDD subtypes, advancing our understanding of their comorbidity at the network level. Notably, FC in the left cuneus was strongly correlated with information processing speed. At the same time, serum FT3 levels were

Table 1 Participant demographics and clinical characteristics of the study participants

Items	nSHypo-MDD $n=29$	SHypo-MDD $n=29$	SHypo $n=26$	HCs $n=29$	$F/\chi^2/t$	p
Age, years	31.6 ± 10.5	33.6 ± 11.8	34.8 ± 12.7	30.4 ± 7.1	0.950	0.419
Gender, male/female	10/19	7/22	6/20	4/25	3.426	0.331
Education, years	14.2 ± 2.2	14.1 ± 2.5	14.4 ± 2.0	15.0 ± 2.3	0.995	0.398
Married, *n* (%)	62.1%	75.9%	53.8%	58.6%	3.235	0.357
Family history of mental illness (Y/N)	8/21	10/19	NA	NA	0.322	0.570
Duration of illness (years)	3.2 ± 1.5	4.1 ± 2.0	NA	NA	1.203	0.275
Medication status (1/0)	12/17	18/11	NA	NA	2.765	0.065
Medication types						
SSRIs	7 (58.3%)	13 (72.5%)	NA	NA	0.625	0.429
SNRIs	5 (41.7%)	5 (27.8%)	NA	NA	NA	NA
HAMD scores	22.1 ± 4.7	23.0 ± 4.0	NA	NA	−0.727	0.470
HAMA scores	13.1 ± 5.6	16.5 ± 7.8	NA	NA	−2.351	0.022*
FT3 (pmol/L)	5.2 ± 2.7	4.8 ± 1.1	4.70 ± 0.5	4.9 ± 0.9	0.665	0.046*
FT4 (pmol/L)	16.8 ± 3.0	15.5 ± 3.7	14.7 ± 2.6	16.4 ± 1.7	2.956	0.031*
TSH (mIU/L)	1.9 ± 0.9	6.1 ± 1.9	7.7 ± 2.8	2.4 ± 0.9	76.666	< 0.001*
Attention						
TMT-A	36.5 ± 12.4	43.7 ± 16.0	37.4 ± 11.1	32.5 ± 8.2	4.154	0.001*
Processing speed						
DSST	48.9 ± 7.1	51.9 ± 12.6	52.2 ± 8.8	60.0 ± 7.8	5.731	0.001*
Verbal memory						
WMS-LM	9.9 ± 2.6	10.1 ± 2.7	10.3 ± 2.6	10.5 ± 2.7	0.299	0.340
Visual memory						
WMS-FM	14.9 ± 2.0	14.6 ± 3.2	15.5 ± 2.7	15.6 ± 2.4	1.044	0.003*
Cognitive flexibility						
TMT-B	61.0 ± 22.0	62.0 ± 31.6	52.0 ± 15.3	51.6 ± 15.4	1.786	0.001*
Working memory						
DSB	6.6 ± 1.2	6.2 ± 1.6	6.7 ± 1.3	7.4 ± 1.2	4.341	0.001*

MDD Major depressive disorder, *nSHypo* not comorbid with subclinical hypothyroidism, *HCs* Healthy controls, *FT3* Free triiodothyronine, *FT4* Free thyroxine, *TSH* Thyroid-stimulating hormone, *HAMD* Hamilton Rating Scale for Depression, *HAMA* Hamilton Rating Scale for Anxiety, *TMT-A* Trail Making Test A, *DSST* Digital Symbol Substitution Test, *WMS-LM* Logical memory subset of the Wechsler Memory Scale, *WMS-FM* Figural memory subset of the Wechsler Memory Scale, *TMT-B* Trail Making Test B, *DSB* Digit Span Backward; comparisons were conducted using MANCOVA tests (*F*), *t*-tests (*t*), and chi-squared tests (χ^2). 0 = drug naive, 1 = under medication.
*$p < 0.05$

inversely associated with FC in the SMA.R. These findings suggest that SHypo-MDD patients may rely on neural compensation to mitigate the neurocognitive impairments associated with SHypo.

Recent extensive cross-sectional research has found that people with a diagnosis of MDD and comorbid SHypo exhibit distinct characteristics, such as increased body mass index (BMI) [49, 51, 53], metabolic dysregulation [27], heightened anxiety symptoms [43], and increased susceptibility to suicidal behaviors [36]. The findings of our study may enhance the comprehension of the clinical features of patients with multiple health conditions. We observed that SHypo-MDD patients had higher HAMA scores than the nSHypo-MDD group, consistent with prior research [21, 43]. A different research study discovered that increased levels of TSH in the blood were linked to higher anxiety levels in people with MDD [44]. Individuals diagnosed with MDD often mention feelings of unease and physical symptoms, which can also be present in various mental and physical disorders, including SHypo [3, 5]. THs can affect the brain and autonomic nervous system, linking SHypo to anxiety and physical symptoms [11]. THs also can regulate mood and brain development by acting on limbic system receptors and influencing hippocampal BDNF levels and serotonin signaling [6, 28, 30]. The study suggests that SHypo may exacerbate anxiety in people with MDD, leading to more severe symptoms. Addressing SHypo could help manage MDD and its symptoms. Previous research has shown that treating SHypo with levothyroxine can improve mood, cognitive abilities, and quality of life in patients with MDD [3, 48].

While cognitive impairments are a well-established feature of MDD, as demonstrated in prior studies [20, 34],

Table 2 Results of two-way ANOVA for neurocognitive characteristics

Items	Interaction		Main effects			
	Diagnosis*SHypo		Diagnosis		SHypo	
	F	Sig	*F*	Sig	*F*	Sig
Attention						
TMT-A	0.926	0.338	5.416	0.022*	4.495	0.036*
Processing speed						
DSST	8.050	0.005*	10.316	0.002*	0.860	0.356
Verbal memory						
WMS-LM	0.168	0.683	0.721	0.398	0.093	0.761
Visual memory						
WMS-FM	0.254	0.616	2.806	0.097	0.023	0.879
Cognitive flexibility						
TMT-B	0.165	0.685	5.637	0.019*	0.235	0.629
Working memory						
DSB	0.337	0.563	6.523	0.012*	3.282	0.073

TMT-A Trail Making Test A, *DSST* Digital Symbol Substitution Test, *WMS-LM* Logical memory subset of the Wechsler Memory Scale, *WMS-FM* Figural memory subset of the Wechsler Memory Scale, *TMT-B* Trail Making Test B, *DSB* Digit Span Backward. *$p < 0.05$

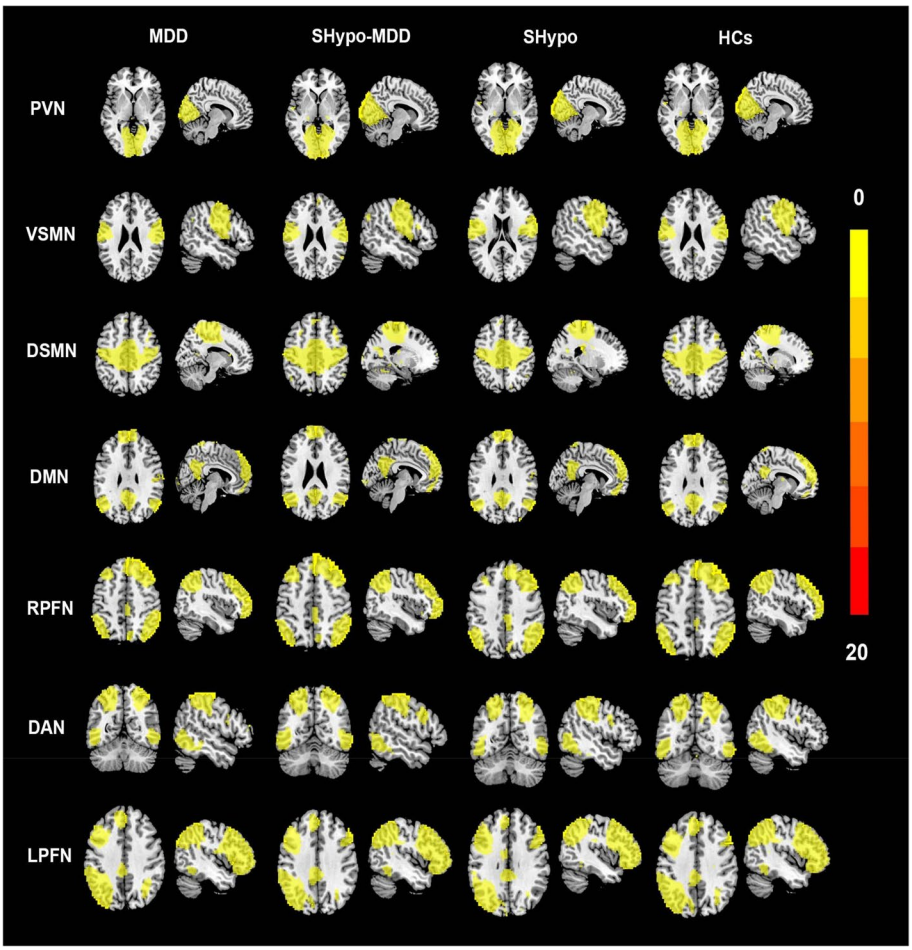

Fig. 1 Spatial maps of PVN, VSMN, DSMN, DMN, RPFN, DAN, and LPFN in the four groups ($p < 0.05$, FDR corrected)

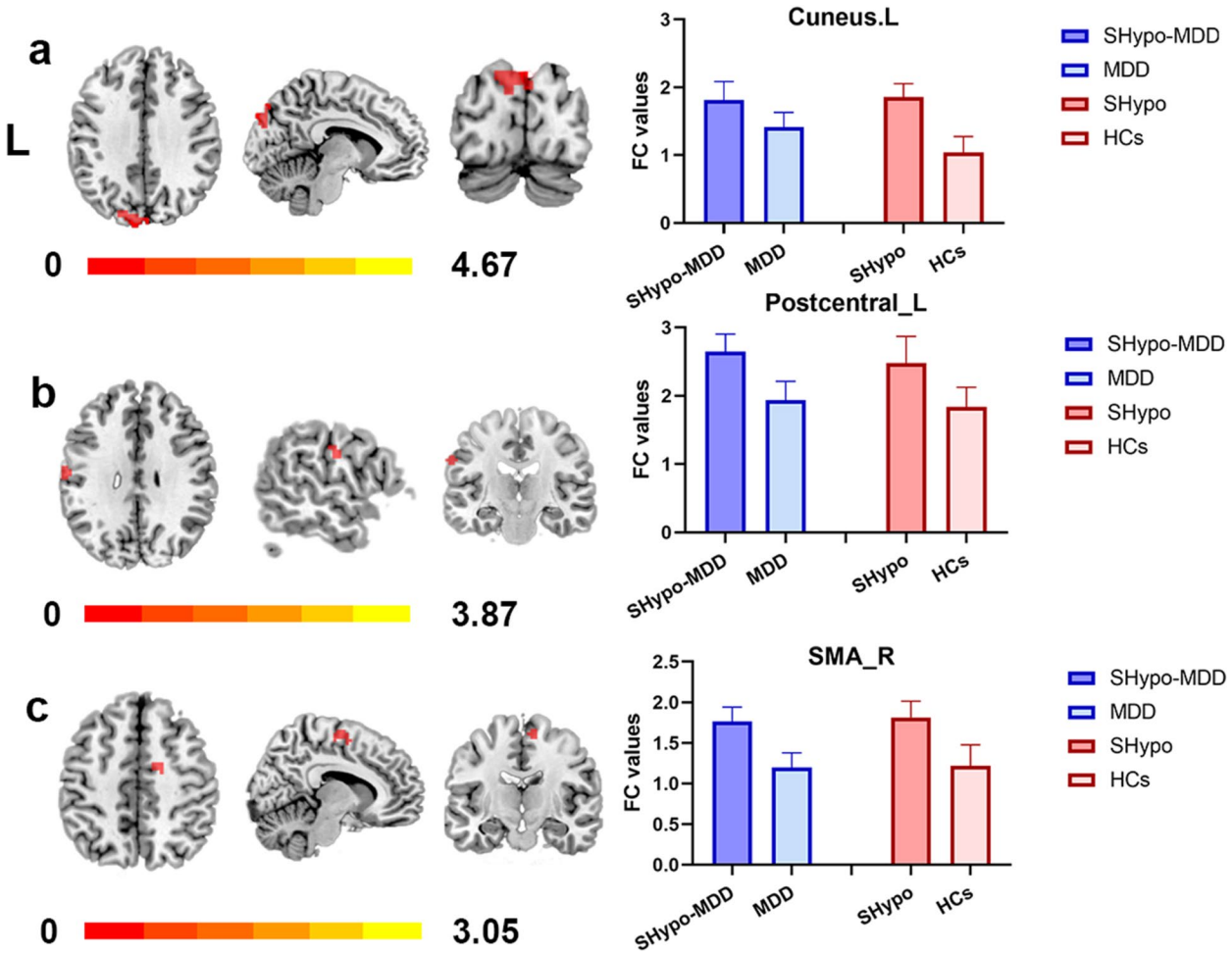

Fig. 2 Significant interaction effects in the left cuneus (**a**). Significant main effect of SHypo in the left postcentral gyrus (**b**), right supplementary motor area (**c**). SMA supplementary motor area

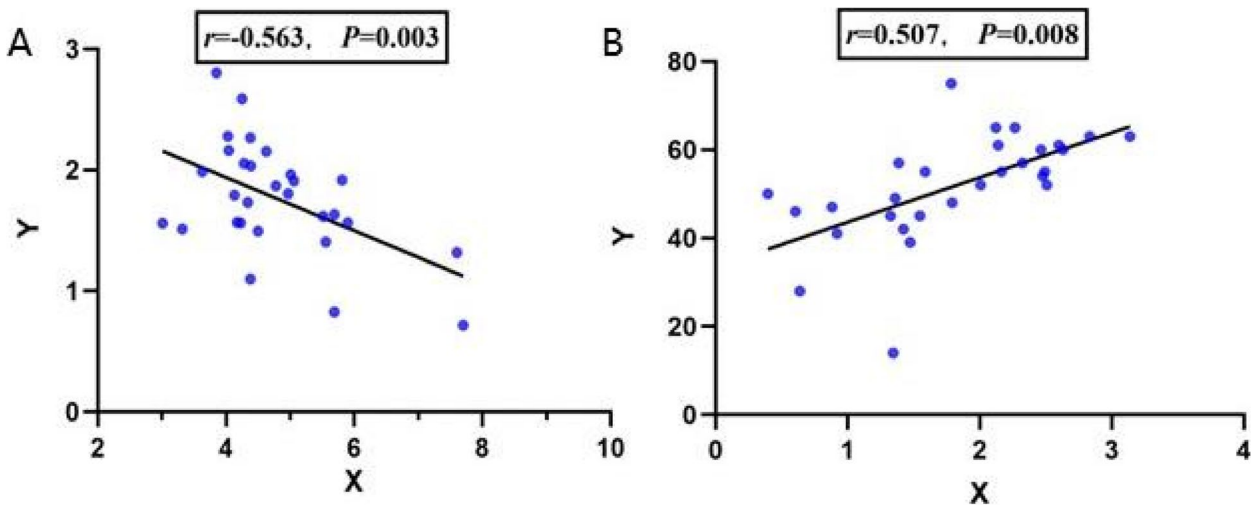

Fig. 3 The partial correlation between serum FT3 levels (X-axis) and the FC value of the SMA.R (Y-axis) in SHypo-MDD patients (**A**), the partial correlation between the FC value of the left cuneus (X-axis) and the DSST scores (Y-axis) in SHypo-MDD patients (**B**)

Table 3 Interaction and main effects of intranetwork connectivity changes among the four groups

Peak location	Hemisphere	Cluster size (voxels)	Peak MNI coordinates			*T* values
			x	y	z	
Main effect of SHypo						
Postcentral	L	31	−60	−15	33	4.73[a]
Supplementary motor area	R	60	9	−12	63	4.40[a]
Interaction						
Cuneus_L	L	33	−9	−87	36	4.67[a]

x, y, and z are the coordinates of primary peak locations in the MNI space; *T* values, statistical value of peak voxel showing FC differences among the four groups; *L*, left; *R*, right; a, the *t* statistical value.

our findings contribute additional evidence by isolating the specific effects on attention, processing speed, cognitive flexibility, and working memory were affected. These results reinforce that MDD-associated cognitive deficits significantly impact daily functioning and highlight the importance of addressing these impairments in treatment strategies.

Moreover, the primary impacts of SHypo were observed in attention and working memory, potentially linked to the condition itself. Cognitive impairment associated with SHypo commonly manifests within a broader psychopathological framework, including challenges with concentration, mood fluctuations, and executive functioning. A study found that individuals with SHypo had slower reaction times and lower accuracy in performance, suggesting a decline in attentional abilities [46]. A recent study has discovered that individuals with thyroid dysfunction exhibit deficiencies in their alerting networks, as demonstrated by the attention network test [47]. Moreover, Zhu et al. observed decreased activation in the bilateral DLPFC during n-back tasks using fMRI, indicating that SHypo patients showed compromised executive function [54].

Our study identified significant main effects of SHypo in the VSMN and DSMN among the four groups. In particular, SHypo-MDD individuals showed higher FC values in the left postcentral gyrus and the SMA.R than nSHypo-MDD individuals. The results align with prior research emphasizing the impact of SHypo on changing the connectivity of brain networks. For instance, SHypo has been associated with disrupted connectivity in networks responsible for sensory processing and motor control, which can exacerbate depressive symptoms and cognitive deficits [19, 46]. The postcentral gyrus, involved in processing bodily sensations, might play a role in the somatic symptoms of anxiety observed in SHypo-MDD patients [14]. Our earlier study discovered increased regional homogeneity (ReHo) levels in the left postcentral gyrus of SHypo-MDD individuals, indicating improved local coordination of neural activity (S. [50, 52]). This increased activity in the postcentral gyrus may also contribute to the high anxiety levels observed in these patients, as the region processes bodily sensations, leading to heightened awareness and sensitivity to these sensations, which is a hallmark of anxiety symptoms [18].

The SMA is crucial in planning and coordinating voluntary movements and in higher-order motor control and cognitive processes related to movement [25]. The increased FC in the SMA.R observed in SHypo-MDD patients indicates that this area might try to make up for impairments resulting from the combination of SHypo and MDD, potentially trying to preserve motor and cognitive abilities despite the underlying disturbances. Furthermore, it was discovered that serum FT3 levels in patients with SHypo-MDD were inversely correlated with the FC values of the right SMA.R. FT3, the bioactive form of thyroid hormone, plays a vital role in controlling brain metabolism and neuroplasticity. Although few genes in adult brain tissue respond to THs, they influence the brain's structure and function [17]. The SMN, encompassing regions involved in processing and integrating sensory and motor information, is essential for executing coordinated movements and maintaining motor skills [7, 33]. Interferences in the SMN can significantly affect a person's capacity to complete daily activities and might play a role in the overall symptoms seen in SHypo-MDD individuals. The changes in SMN connectivity, especially the higher FC in the SMA.R, demonstrate how the network is affected by TH imbalances and how they may worsen motor and cognitive symptoms.

Moreover, the significant interaction effect between SHypo and MDD on DSST scores underscores the complex interplay between thyroid function and depressive symptoms on cognitive performance. The DSST scores were significantly lower in SHypo vs HCs, indicating pronounced cognitive impairments. However, in SHypo-MDD vs nSHypo patients, this effect was less pronounced, suggesting potential compensatory mechanisms at play. Moreover, there was a notable interaction effect between SHypo and MDD in the PVN, where

SHypo-MDD patients showed higher FC values in the left cuneus compared to nSHypo-MDD patients, and these values were positively correlated with DSST scores. The cuneus within the occipital lobe is essential in visual and cognitive functions such as attention and spatial processing [2, 13]. The increased FC in the cuneus on the left side seen in patients with SHypo and MDD indicates potential compensatory processes to address cognitive impairments linked to both conditions.

Moreover, the positive association between cuneus FC values and DSST scores indicates that enhanced visual network connectivity supports cognitive performance. This observed interaction effect may suggest a compensatory neural mechanism in which the cuneus augments its connectivity to counteract the detrimental cognitive effects of SHypo and MDD. The cuneus appears to support cognitive function through heightened involvement in visual and spatial processing tasks, as indicated by performance on the DSST. This adaptive increase in connectivity likely signifies the brain's endeavor to uphold cognitive abilities in the face of the combined influence of SHypo and MDD.

Limitation

This study had numerous constraints. The study employed a cross-sectional approach, capturing a brief moment to assess the patient's condition. As a result, it precluded the examination of any possible changes in the patient's condition over a while. Even after adjusting for age, gender, and education as factors, unmeasured variables may still potentially affect the outcomes. Subsequent studies may benefit from investigating additional covariates or utilizing more sophisticated statistical techniques to mitigate this limitation. Without assessing the treatment's effect on the patient's conditions, it is uncertain if the differences between the groups are due to SHypo or other factors. The study only included individuals with SHypo, so the findings may not apply to those with severe hypothyroidism. Another limitation of this study is the absence of BMI data, which prevented us from accounting for its potential influence on TSH levels. Prior studies have shown significant associations between BMI and TSH, suggesting BMI could be a confounding factor [32, 39].

Additionally, while we discussed increased susceptibility to suicidal behaviors in SHypo-MDD patients, the lack of Suicide Severity Index (SSI) data limited our ability to analyze its relationship with brain functional connectivity. Future studies should incorporate BMI and SSI data to enhance the robustness and depth of findings. Finally, antidepressants and thyroid hormone medications influence cognitive function and brain connectivity [9, 12]. While medication status was recorded in our study, the small sample size limited our ability to perform subgroup analyses based on specific medication types or dosages. This represents a limitation, as the potential impact of these medications on our findings cannot be excluded. Future research should explore the specific effects of these medications on brain networks in comorbid SHypo-MDD patients.

Conclusions

In conclusion, our study highlights significant FC changes in SHypo-MDD patients, particularly in the PVN, VSMN, and DSMN. Increased FC in the left cuneus was associated with better cognitive performance, suggesting compensatory mechanisms mitigating cognitive deficits. These findings underscore the complex interplay between SHypo and MDD, emphasizing the need for integrated management of SHypo and MDD comorbidity to improve cognitive outcomes. Future research should further explore these neural compensatory processes and their potential therapeutic implications.

Abbreviations

MDD	Major depressive disorder
SHypo	Subclinical hypothyroidism
FC	Functional connectivity
RSNs	Resting-state networks
VSMN	Ventral sensorimotor network
DSMN	Dorsal sensorimotor network
PVN	Pole visual network
FT3	Free triiodothyronine
FT4	Free thyroxine
TSH	Thyroid-stimulating hormone
SMA.R	Right supplementary motor area
DSST	Digit symbol substitution test
THs	Thyroid hormones
DLPFC	Dorsolateral prefrontal cortex
EF	Executive functioning
VBM	Voxel-based morphometry
GMV	Gray matter volume
rs-fMRI	Resting-state functional magnetic resonance imaging
PFC	Prefrontal cortex
ACC	Anterior cingulate cortex
ReHo	Regional homogeneity
ICA	Independent component analysis
SMN	Sensorimotor network
RAN	Anterior network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
HDRS	Hamilton Depression Rating Scale
HAMA	Hamilton Anxiety Scale
TMT	Trail Making Test
LM	Logical memory
FM	Figural memory
WMS-R	Wechsler Memory Scale-Revised
DSB	Digit Span Backward
CSF	Cerebrospinal fluid
WM	White matter
MANCOVA	Multivariate Analysis of Covariance
ROIs	Regions of interest
BMI	Body mass index

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Authors' Contribution
S.Z. and Q.L. designed the study. J.W. and X.L. performed the experiments. Y.D., X.W., and Y.X. analyzed the data. H.S. and H.Z. prepared the figures. X.W., Z.C., and R.Y. conducted the literature review. S.Z. and Z.Y. wrote the main manuscript text. Q.L. and Z.Y. reviewed and edited the manuscript. All authors reviewed the final version of the manuscript

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The research protocol received approval from the Ethics Committee of the Affiliated Nanjing Brain Hospital at Nanjing Medical University (No. 83230260) in adherence to the principles outlined in the Declaration of Helsinki. All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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