Alpha Psychiatry

Alpha Psychiatry **2026**; 27(6): 52317
https://doi.org/10.31083/AP52317

Original Article

Aberrant Serotonin Transporter-Enriched Functional Connectivity in Mild Cognitive Impairment Patients With Depressive Symptoms

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Academic Editor: Takahiro Nemoto
Submitted: 27 March 2026 Revised: 26 June 2026 Accepted: 14 July 2026 Published: 9 November 2026

Abstract

Background: Neurotransmitter function is closely associated with both the development and treatment of depression. The Receptor-Enriched Analysis of Functional Connectivity by Targets (REACT) method enhances functional magnetic resonance imaging (fMRI) analyses by integrating molecular information on neurotransmitter systems, thereby providing a biologically informed perspective on functional connectivity (FC). **Methods:** In this study, we used the REACT method to investigate neurotransmitter-related FC abnormalities in patients with mild cognitive impairment (MCI) and depressive symptoms (D-MCI). Resting-state fMRI data were acquired from 117 participants using a 3-T MRI scanner, including 31 patients with D-MCI, 40 patients with MCI without depression (nD-MCI), and 46 healthy controls (HCs). Differences in neurotransmitter-related FC strength among the three groups were examined using analysis of covariance, followed by Tukey's post hoc tests. Pearson correlation analyses were subsequently performed to evaluate the associations between neurotransmitter-related FC values in brain regions showing significant group differences and clinical variables. **Results:** Compared with the nD-MCI group, the D-MCI group exhibited decreased serotonin transporter-enriched FC in the left superior medial frontal gyrus. Relative to the HC group, the D-MCI group showed increased serotonin transporter-enriched FC in the left precuneus lobe and right superior frontal gyrus. **Conclusions:** These findings suggest that patients with D-MCI exhibit abnormalities in the serotonin transporter-related functional network, providing a novel perspective on the neural mechanisms underlying depressive symptoms in individuals with MCI.

Keywords: mild cognitive impairment; depression; functional magnetic resonance imaging; Receptor-enriched analysis of functional connectivity by targets

Main Points

1. Using REACT, this study identified selective abnormalities in serotonin transporter (SERT)-enriched functional connectivity (FC) in patients with mild cognitive impairment and depressive symptoms (D-MCI). Among nine neurotransmitter/receptor systems examined, only SERT-enriched FC differed significantly among D-MCI, nD-MCI, and healthy controls, suggesting that serotonergic circuits may be preferentially vulnerable in the early neurodegenerative stage of D-MCI.

2. D-MCI patients exhibited a bidirectional pattern of SERT-enriched FC abnormalities within the default mode network (DMN): decreased SERT-enriched FC in the left superior medial frontal gyrus relative to nD-MCI, and increased SERT-enriched FC in the left precuneus and right superior frontal gyrus relative to healthy controls. These regions are key DMN nodes involved in self-referential processing, episodic memory, and cognitive control, linking serotonergic dysregulation to depressive symptoms in MCI.

3. SERT-enriched FC metrics may serve as promising neuroimaging biomarkers for D-MCI. Reduced SERT-enriched FC in the left superior medial frontal gyrus may help distinguish D-MCI from nD-MCI, while aberrant SERT-enriched FC in the precuneus and superior frontal gyrus may reflect a targetable serotonergic endophenotype. Given that antidepressant response correlates with SERT occupancy, baseline SERT-enriched FC patterns could aid in stratifying MCI patients with comorbid depression and predicting SSRI treatment response, although prospective longitudinal validation is required.

1. Introduction

Mild cognitive impairment (MCI) is considered an intermediate state between normal ageing and dementia. Al-

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though not everyone with MCI will develop dementia, this population is at a higher risk of developing Alzheimer's disease (AD) and other forms of dementia [1]. Depressive symptoms are the most common psychobehavioural manifestation in patients with MCI, affecting 32% of individuals. Those with MCI and depression (D-MCI) have a higher rate of progression to AD than those without depression, with rates of 31% and 13.5%, respectively [2]. However, the pathogenesis of D-MCI remains unclear.

Emerging evidence suggests that depressive symptoms in MCI may exacerbate neurodegeneration via glucocorticoid-mediated hippocampal atrophy and neuroinflammation [3,4]. However, the serotonergic correlates of this comorbidity remain underexplored. Depression is associated with a deficiency of monoamine neurotransmitters and abnormal functioning of their receptors. Disruptions affecting the three main neurotransmitter systems—serotonin, norepinephrine, and dopamine—can impact various brain regions [5]. The superior medial frontal region is particularly sensitive to changes in serotonin. Compared with carriers of the long A allele (LA) (whether homozygous or heterozygous) of the serotonin transporter-linked polymorphic region, children and adolescents who are homozygous for the S allele exhibit weaker connectivity in the superior medial frontal cortex [6]. Furthermore, antidepressants achieving 70% or greater serotonin transporter (SERT) occupancy in the striatum, thalamus, limbic regions (e.g., amygdala and hippocampus), and the precuneus lobe are associated with greater improvements in both depressive symptoms and visuospatial memory performance [7].

Many studies have used blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to assess functional brain activity in patients with depressive symptoms. In BOLD imaging, neuronal activation leads to increased oxygen consumption, which in turn drives an increased influx of oxygenated blood and a subsequent rise in the BOLD signal [8]. Relative to healthy controls, depressed patients exhibit heightened functional connectivity within dorsomedial prefrontal cortex hubs that subserve cognitive control, default-mode, and affective networks [9]. Meta-analytic evidence further pinpoints significant group differences in the left amygdala, right insula, right orbitofrontal cortex, and precuneus [10]. Nevertheless, standard BOLD-based fMRI approaches are inherently unable to capture molecular-level information regarding neurotransmitter systems.

The recently introduced REACT (Receptor-enriched Analysis of Functional Connectivity by Targets) approach overcomes this shortcoming by allowing the construction of molecularly enriched networks. Specifically, molecular-enriched functional connectivity (FC) quantifies the interaction between each brain region or voxel and those areas that exhibit a high density of particular receptor types. This framework thus offers a basis for elucidating how neurotransmitter systems—as indexed by their receptor distributions—shape large-scale connectivity patterns [11,12].

In this study, we used REACT to investigate abnormalities in neurotransmitter-related molecular-enriched functional networks in patients with D-MCI. We hypothesized that, compared with MCI patients without depression (nD-MCI) and healthy controls (HC), patients with D-MCI exhibit abnormal molecular-enriched functional networks in mood-related brain regions.

2. Materials and Methods

2.1 Patients

From July 2017 to August 2022, we enrolled healthy controls, patients with MCI without depressive symptoms, and those with MCI and depressive symptoms from Tongde Hospital in Zhejiang Province. Cognitive function was assessed by trained psychiatrists using the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) scale; MCI was defined as MMSE >24 and CDR = 0.5 [13]. Depressive symptoms were evaluated per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, with clinically significant depression determined by a Neuropsychiatric Inventory score >4 [14,15] and a 17-item Hamilton Rating Scale for Depression (HAMD-17) score >7 [16,17]. Exclusion criteria included left-handedness, current use of antidepressant medications, a history of drug use, psychotic or bipolar disorders, cerebrovascular diseases, Parkinson's disease, sleep disorders, chronic organic diseases, and long-term use of adjunctive medications. All participants provided written informed consent in accordance with the requirements of the Ethics Committee of Tongde Hospital of Zhejiang Province (approved number 2017-11-12).

2.2 MRI Scanning

The individuals underwent an MRI scan with a Siemens Magnetom Verio 3.0 Tesla scanner (Siemens Medical Systems, Erlangen, Germany). Resting-state fMRI was performed using the echo-planar imaging process with the following settings: There were 33 axial slices with 4.8/0 mm thickness/gap, 64 × 64 in-plane resolution, 2000 ms repetition time, 30 ms echo time, 90° flip angle, 200 × 200 mm^2 field of view, and 200 volumes. We obtained high-resolution inversion time (T1)-weighted images using a three-dimensional magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence with the following parameters: inversion time/repetition time (TR)/echo time (TE) = 900/1900/2.48 ms, flip angle = 9°, 128 slices, field of view (FOV) = 256 × 256 mm^2, and 1 × 1 × 1 mm^3 resolution. Participants were instructed to relax with their eyes closed during scanning.

2.3 Data Processing

The Data Processing and Analysis for Brain Imaging (DPABI) toolkit version 6.2 (rfmri.org) was used to pre-

process resting-state functional magnetic resonance imaging data. To establish magnetic field balance, the first 10 time points were deleted. The remaining data were analyzed using slice timing and motion correction. Regarding the motion correction, each participant had a maximum displacement of less than 2 mm in the x-, y-, or z-axes, with 2 angular motions. Data with head motion frame-to-frame displacement (FD) exceeding 0.3 were removed. The high-resolution T1 anatomical scans of each participant were then co-registered with the fMRI images, which were subsequently standardized to the Montreal Neurological Institute (MNI)152 template. The normalized image was blurred using a 6-mm full-width Gaussian kernel set to half-maximum. The smoothed fMRI images underwent linear detrending and temporal bandpass filtering (0.01–0.08 Hz). The time series for each voxel was then regressed to remove white matter, cerebrospinal fluid, and Friston-24 head motion distortions.

2.4 Molecular-Enriched Functional Connectivity Analysis With REACT

Neurotransmitter positron emission tomography (PET) atlases were used as spatial priors for the enriched resting-state fMRI analysis. These PET atlases are derived from publicly available software that has been widely used in multimodal neuroimaging studies [11]. The following transporter and receptor density maps were included: 5-HT1A (serotonin 5-hydroxytryptamine receptor subtype 1A), 5-HT1B (5-HT receptor subtype 1B), 5-HT2A (5-HT receptor subtype 2A), D1 (dopamine D1 receptor), D2 (dopamine D2 receptor), DAT (dopamine transporter), NAT (noradrenaline transporter), and SERT (serotonin transporter). In addition, an FDOPA PET map reflecting dopamine synthesis capacity was included. The original templates can be accessed at https://github.com/netneurolab/neuromaps [11].

Prior to this, each PET atlas was masked using a common grey matter mask and its image values were scaled between 0 and 1 [11]. We performed Receptor-enriched analysis of functional connectivity using the REACT toolbox (https://github.com/ottaviadipasquale/react-fmri). REACT uses two-step multiple regression analysis to estimate neurotransmitter-related functional circuits. To restrict the analysis to the voxels where neurotransmitter density information is available, first mask the fMRI volume using a binarized mask created from the molecular template. The fMRI images are then weighted using the molecular template as a set of spatial regressors, which also estimates the main fluctuations linked to each chemical system at the subject level. The subject-specific spatial map linked to each molecular template is then estimated in the second multiple regression analysis using the resulting subject-specific time series as a time regressor. Each subject's neurotransmitter profile and an fMRI dataset that represents the molecularly enriched FC linked to a particular neurotransmitter make up the output [11].

2.5 Statistical Analysis

Statistical analyses of clinical and demographic features were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Differences in sex distribution among groups were evaluated using the chi-square test, while variations in age and education level were assessed using analysis of variance (ANOVA) and two-sample *t*-tests.

Molecular-enriched FC maps associated with different neurotransmitters were examined using the DPABI toolkit. A one-way analysis of covariance (ANCOVA) was performed voxel-by-voxel to compare the molecular-enriched FC maps of the three groups for each of the following neurotransmitters and receptors: 5-HT1A, 5-HT1B, 5-HT2A, D1, D2, DAT, F-DOPA, NAT, and SERT. Pairwise group comparisons were subsequently conducted using Tukey's post hoc *t*-tests. Age, sex, and mean relative head displacement were included as covariates in the ANCOVA model, and post hoc analyses were performed to ensure the validity of the findings. Multiple comparison correction was carried out using 3dClustSim, with the significance threshold set at $p < 0.05$ (corresponding to an individual voxel threshold of $p < 0.005$ and a minimum cluster size of 50 voxels). As this was an exploratory analysis across nine neurotransmitter systems, multiple comparison correction (3dClustSim) was applied separately within each neurotransmitter model, and no cross-neurotransmitter family-wise error correction was performed. Finally, Pearson correlation analyses were performed to examine the relationships between molecular-enriched FC values in brain regions showing significant group differences and clinical variables, with statistical significance set at $p < 0.05$.

3. Results

3.1 Neuropsychological Results

Demographic and clinical characteristics are summarized in Table 1. Across the three groups, no significant differences were observed for age ($F = 1.1$, $p = 0.320$), gender distribution ($\chi^2 = 6.0$, $p = 0.191$), or education level ($F = 0.7$, $p = 0.467$). In contrast, the D-MCI group scored significantly higher than the nD-MCI group on both the HAMD-17 and the depression domain of the Neuropsychiatric Inventory (D-NPI) (ANOVA: $F = 224.1$, $p < 0.001$ and $F = 178.3$, $p < 0.001$, respectively). No significant difference in MMSE scores emerged between the nD-MCI and D-MCI groups ($t = 0.03$, $p = 0.971$). Likewise, the nD-MCI and healthy control groups did not differ significantly on the HAMD-17 ($t = –0.1$, $p = 0.132$) or the NPI ($t = –0.4$, $p = 0.736$). We used the MATLAB2019b (MathWorks, Massachusetts) script 'Sampsizepwr' to calculate the statistical power, which was 80% at an alpha level of 0.05.

Table 1. Demographics and neuropsychological data.

	D-MCI group	nD-MCI group	HC group	F/χ^2 value	p value
Gender, n (M/F)	31 (13/18)	40 (17/23)	46 (22/24)	6	0.191
Age, years	66.7 ± 8.1	68.9 ± 9.3	69.7 ± 7.1	1.1	0.320
Education, years	10.7 ± 2.6	10.9 ± 2.8	10.5 ± 3.1	0.7	0.467
CDRSB	0.6 ± 0.5	0.7 ± 0.5	0 ± 0	37.5	<0.001
MMSE	26.6 ± 1.1	26.5 ± 1.0	29.2 ± 0.9	38.3	<0.001
HAMD	11.7 ± 3.1	1.0 ± 1.6	0.9 ± 0.9	224.1	<0.001
D-NPI	7.19 ± 2.3	1.1 ± 1.6	0.6 ± 0.8	178.3	<0.001

Data are represented as means ± standard deviations. The chi-squared test was used to compare sex, and one-way analyses of variance with post hoc two-sample *t*-tests were used to compare age and neuropsychological data. HC, healthy controls; D-MCI, mild cognitive impairment with depression; nD-MCI, no depression and mild cognitive impairment; M, Male; F, Female; MMSE, Mini-Mental State Examination; CDRSB, clinical dementia rating-sum of boxes; D-NPI, depression domain of the Neuropsychiatric Inventory; HAMD, Hamilton Depression Rating Scale.

Table 2. Brain regions with significantly different serotonin transporter-enriched functional connectivity in the mild cognitive impairment with depression group compared with the non-depressed mild cognitive impairment and healthy controls groups.

Brain regions	Voxels	BA	MNI coordinates			F/T value
			x	y	z	
D-MCI vs nD-MCI						
Left superior medial frontal gyrus	60	9	–9	51	33	–4.0
D-MCI vs HC						
Left precuneus lobe	79	5	–3	–48	60	4.2
Right superior frontal gyrus	72	6	15	6	54	4.2

MNI, Montreal Neurological Institute; BA, Brodmann area.

3.2 Molecular-Enriched Functional Connectivity in the D-MCI Group

Following multiple comparison correction, only SERT-related molecular-enriched functional connectivity exhibited significant differences between the three groups. In the left superior medial frontal gyrus, the D-MCI group exhibited lower serotonin transporter-enriched functional connectivity than the nD-MCI group. The D-MCI group exhibited increased SERT-enriched FC in the right superior frontal gyrus and left precuneus lobe compared to healthy controls (Fig. 1, Table 2). There is a weak negative correlation in D-MCI patients between SERT-enriched functional connectivity values in the left precuneus lobe and Hamilton Rating Scale for Depression scores (r = –0.3231, p = 0.0762) (Fig. 2).

4. Discussion

This study employed the REACT method to investigate the relationship between receptor density distribution and functional connectivity patterns in patients with D-MCI. Multiple neurotransmitter atlases were used in the REACT analysis, yet only serotonin transporter-enriched FC showed statistically significant differences between groups. The brain regions exhibiting significant differences were the left precuneus lobe, the left medial prefrontal lobe, and the right superior frontal gyrus.

The medial frontal gyrus and the precuneus, two principal nodes of the default mode network (DMN), are functionally interconnected, with the latter playing a pivotal role in integrating mental processes through its support of cognitive control functions, including visual imagery, episodic memory, and autonomous operations. Reduced intra-DMN FC between the precuneus lobe/posterior cingulate cortex (PCC) and the bilateral angular gyrus is associated with abnormally excessive autobiographical memory in drug-naïve, first-episode major depressive disorder (MDD) [18]. In a study of 125 unmedicated patients with depressive symptoms, FC between the precuneus lobe and several regions—including the lateral orbitofrontal cortex, dorsolateral prefrontal cortex, temporal cortex, and angular gyrus—was increased. However, in medicated patients, FC between the lateral orbitofrontal cortex and the precuneus lobe decreased to levels comparable to those of the control group [19]. Compared with healthy controls, the depression group showed significantly increased gray matter volume in the ventromedial prefrontal cortex, parahippocampal gyrus, amygdala, right superior parietal lobe, and the left ventral portion of the precuneus lobe. Furthermore, these gray matter volume changes associated with depres-

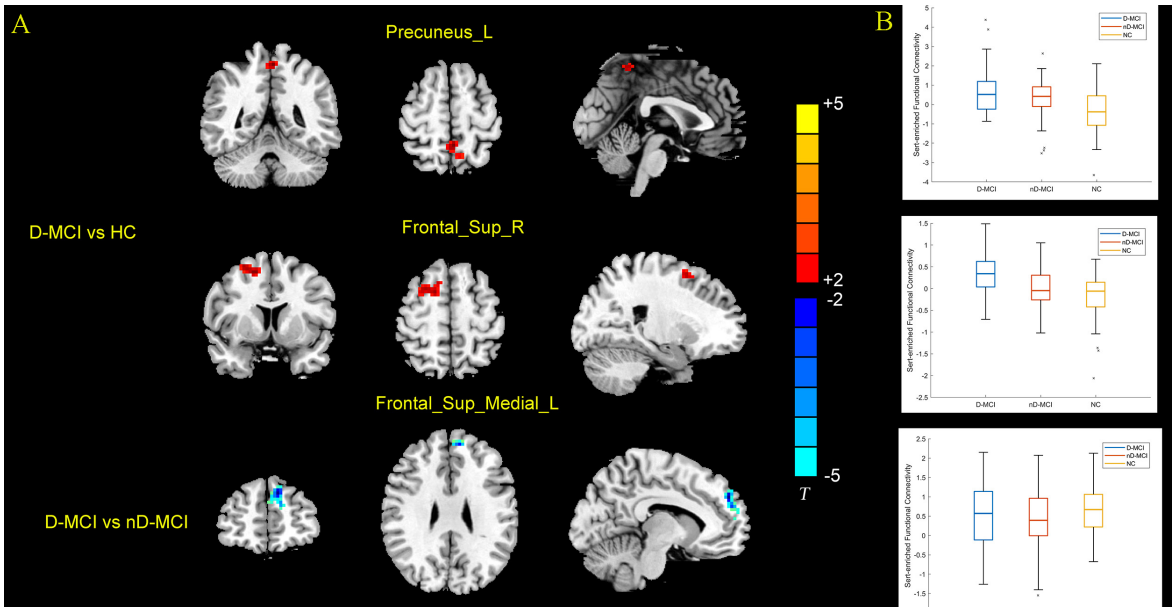


Fig. 1. Brain regions with significantly different serotonin transporter-enriched FC values in the D-MCI group compared with the nD-MCI and HC groups. (A) Standard atlas localization of abnormal brain regions. (B) Mean and standard deviation of abnormal brain regions. Compared with the nD-MCI, the D-MCI group showed decreased serotonin transporter-enriched FC in the left superior medial frontal gyrus. Compared with healthy controls, the D-MCI group showed increased serotonin transporter-enriched FC in the left precuneus lobe and right superior frontal gyrus. FC, functional connectivity. Precuneus_L: left precuneus; Frontal_Sup_R: right superior frontal gyrus; Frontal_Sup_medial_L: left superior medial frontal gyrus. An asterisk indicates a deviation from the mean.

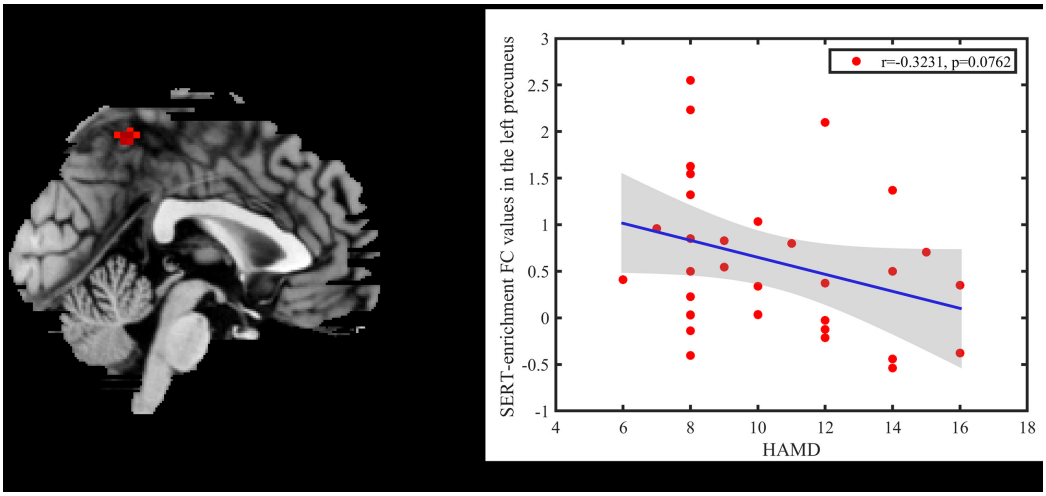


Fig. 2. In D-MCI patients, there was a weak negative correlation between the SERT-enrichment functional connectivity values in the left precuneus lobe and the Hamilton Rating Scale for Depression scores (r = –0.3231, *p* = 0.0762). The scatter plot includes the fitted regression line with 95% confidence intervals.

sion were spatially correlated with serotonin receptor distributions (5-HT1A, 5-HT1B, and 5-HT2A) [20].

The serotonergic system projects broadly across cortical regions, including the precuneus, posterior cingulate gyrus, lingual gyrus, and fusiform cortex, and also extends anteriorly to the medial frontal cortex and parahippocampal gyrus [21]. Activity in the medial prefrontal cortex during self-referential processing is associated with rumination, and abnormalities in this region have been consistently observed in depression [22]. Compared with healthy controls, medication-naïve adolescents with MDD exhibited reduced emotion-related deactivation of the medial prefrontal cortex and posterior cingulate gyrus, along with enhanced emotional dependence of these regions, as reflected by increased functional connectivity in the anterior precuneus, cingulate gyrus, and striatum/inferior cingulate gyrus [23]. Across all participants, greater activation of the posterior cingulate cortex, medial prefrontal cortex, inferior

parietal lobe, and medial temporal gyrus during rumination was associated with higher levels of self-reported rumination and depressive symptoms. Furthermore, adolescents with major depressive symptoms showed greater activation than their healthy peers in brain regions involved in visual, somatosensory, and emotional processing [24]. Although these findings are derived from studies of primary MDD, they may inform our understanding of serotonergic mechanisms in D-MCI, given the shared pathology of the DMN between the two conditions.

In our study, only serotonin transporter (SERT)-enriched functional connectivity was found to be abnormal in patients with D-MCI. SERT is the primary target of many currently prescribed antidepressants and is critically involved in the manifestation of depressive symptoms as well as the response to antidepressant treatment [25]. In long-term medication-free patients and those who are new to antidepressants, SERT binding is reduced, which may reflect either decreased activity or a reduced number of serotonergic neurons in depressed individuals [26].

The SERT-enriched FC abnormalities in D-MCI suggest serotonergic dysregulation within the DMN. Reduced SERT availability may alter 5-HT1A/5-HT2A receptor signaling, contributing to DMN dysfunction and mood dysregulation [25,26]. The left superior medial frontal gyrus is implicated in self-referential processing and rumination, the left precuneus supports episodic memory and visuospatial integration, and the right superior frontal gyrus participates in cognitive control—functions consistently impaired in depression [18,22]. Given that antidepressant response correlates with SERT occupancy in limbic regions [7], SERT-FC metrics in these hubs may represent promising imaging biomarkers for treatment prediction, though longitudinal validation is essential.

The null findings for dopaminergic and noradrenergic systems do not preclude their involvement in D-MCI [27]; rather, they may reflect that SERT-enriched circuits are preferentially vulnerable in the early neurodegenerative stage captured by our MCI cohort [28], whereas catecholaminergic changes become prominent later or in specific subtypes.

The SERT-enriched functional connectivity abnormalities identified herein—reduced SERT-FC in the left superior medial frontal gyrus contrasting with elevated SERT-FC in the left precuneus and right superior frontal gyrus—offer promising translational potential as neuroimaging biomarkers. The left superior medial frontal gyrus demonstrates sensitivity to serotonergic genetic variation and antidepressant occupancy, suggesting that SERT-FC metrics in this region may help distinguish D-MCI from nD-MCI and screen MCI patients at high risk for comorbid depression [6]. Aberrant SERT-FC within the default mode network (precuneus and superior frontal gyrus) may reflect a targetable serotonergic endophenotype underlying both mood dysregulation and cognitive decline. Furthermore, because antidepressant response correlates with SERT occupancy in corticolimbic regions [7], baseline SERT-FC patterns in these hubs could potentially stratify patients for selective serotonin reuptake inhibitor therapy and predict treatment response. Nonetheless, these clinical applications remain hypothetical; prospective longitudinal studies are essential to establish the diagnostic specificity, sensitivity, and predictive validity of these molecular-enriched connectivity markers before translation into routine clinical practice.

Limitations

There are some limitations to our study that need to be mentioned. First, we did not record MCI subtypes at enrollment, which is a methodological limitation, as amnestic MCI may have differential serotonergic vulnerability. The results require multicenter, large-sample data to validate. Second, to validate the predictive value of SERT-FC abnormalities for dementia conversion, a practical longitudinal scheme would entail: (1) annual clinical and neuropsychological follow-up for 3–5 years using MMSE, CDR, and HAMD-17; (2) a second resting-state fMRI at 24 months to track within-subject changes in SERT-FC; and (3) cerebrospinal fluid (CSF) Aβ42/tau or amyloid PET at baseline to stratify participants by AD biomarker status. Conversion to dementia would be defined as CDR global score $\geq$1. Cox proportional hazards models could then test whether baseline SERT-FC in the left precuneus or superior medial frontal gyrus predicts time-to-conversion, independent of age, sex, education, and baseline cognition. Third, the neurotransmitter PET templates used in the study are based on population averages, which may result in discrepancies when applied to individual subjects. Finally, depressive symptoms in D-MCI occur against a backdrop of neurodegenerative disease, and their pathogenesis may involve complex interactions between cognitive decline and emotional regulation pathways, representing a fundamental difference from primary MDD [29]. Future studies should include patients with primary MDD as a control group to clarify the unique neuroimaging features of D-MCI relative to primary depression.

5. Conclusions

This study used the REACT method to reveal the characteristics of neurotransmitter-related, molecular-enriched functional connectivity in patients with D-MCI. The differential brain regions associated with SERT-enriched functional connectivity were found to be mainly located in the default mode network. Our studies provide imaging evidence to support the neural mechanisms underlying depressive symptoms in patients with MCI.

Availability of Data and Materials

All data are available upon request to the corresponding authors.

Author Contributions

ZWG and XZL designed the study. FQW, HTH, CWM and XJC performed the experiments. SLW and ZWG interpreted the results. XZL and XJC analysed the data and were major contributors to the writing of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of Tongde Hospital of Zhejiang Province (approval no. 2017-11-12). All participants gave their written informed consent.

Acknowledgment

Not applicable.

Funding

This research was supported by the General Project of the Department of Science and Technology of Zhejiang Province (2020KY182 to XZ LIU), the General Project of the Department of Science and Technology of Zhejiang Province (2024KY873 to ZW Guo) the Wenzhou Public Welfare Science and Technology Plan Project (Y2023198 to CW Mao), Jinhua Science and Technology Plan Project (No. 2023-4-090 to XJ Chen), and the Jinhua Municipal Hospital Youth Scientific Research Startup Fund Project (JY2022-2-01 to XJ Chen).

Conflicts of Interest

The authors declare no conflicts of interest.

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