Journal of Integrative Neuroscience

J. Integr. Neurosci. **2026**; 25(6): 49751
https://doi.org/10.31083/JIN49751

Original Research

Neural Correlates of Diagnostic-Relevant Emotional Processing in Schizophrenia and Major Depressive Disorder: Insights from a Replication of fMRI and Self-Report Scales

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Academic Editor: Bettina Platt
Submitted: 6 January 2026 Revised: 31 March 2026 Accepted: 17 April 2026 Published: 22 June 2026

Abstract

Background: Accurate differentiation between major depressive disorder (MDD) and schizophrenia (SZ) remains a clinical challenge due to overlapping symptoms and limitations of traditional diagnostic methods. Integrating neurobiological markers, especially functional magnetic resonance imaging (fMRI), with clinical assessments holds promise for improving diagnostic specificity. Recently, a translational cross-validation paradigm integrated the von Zerssen Paranoid–Depression Scale (a clinical self-assessment scale) with simultaneous fMRI data acquisition to cross-validate evaluations of psychopathology using neuroimaging techniques, allowing direct comparison of subjective symptom-related processing with corresponding neural activation patterns. Hence, we sought to replicate this method in an independent Chinese cohort. **Methods**: A sample of 62 participants, comprising 32 MDD and 30 SZ patients, underwent task-based fMRI scanning using a paradigm with statements of diagnostically neutral (DN), depressive-specific (DS), and paranoid-specific (PS) content. After preprocessing, the number was reduced to 57 (30 MDD and 27 SZ). Neural responses were analyzed using the PS versus DS contrast to isolate paranoia- versus depression-related processing. Brain activation patterns were compared across the two patient groups. Mixed-effects Analysis of Variance (ANOVA) was used to test main effects and interactions. **Results**: In SZ relative to MDD, processing paranoia-relevant content (PS > DS) was associated with greater activation in the bilateral supplementary motor area (SMA), left middle cingulate cortex (MCC), right precentral gyrus, and right superior frontal gyrus, indicating differential neural engagement during paranoia-specific processing. The second-level mixed-effects ANOVA revealed a significant main effect of condition (PS versus DS) across both groups in the precuneus/calcarine cortex, left frontal cortex, and hippocampal regions, indicating task-related modulation of neural activity. Importantly, a significant group × condition interaction was identified in fronto-cingulate, motor, temporal, and prefrontal regions, suggesting differential neural responses to paranoia-related processing between SZ and MDD. **Conclusions**: Integrating task-based fMRI with clinical self-assessment scales offers a robust approach to delineate neurofunctional differences between SZ and MDD. Combining self-report scales with fMRI data contributes to the development of objective neurobiological markers, enhances the reliability of the differential diagnosis, and provides a neurobiological basis for more precise clinical assessments.

Keywords: depression; schizophrenia; fMRI; biomarkers; differential diagnosis; paranoia; emotional processing

1. Introduction

Current psychiatric diagnostic systems, such as the International Classification of Diseases (ICD) [1] and the Diagnostic and Statistical Manual of Mental Disorders (DSM) [2], are widely used in clinical practice. However, these systems have been criticized for their limited validity and weak correspondence with underlying neurobiological mechanisms [3]. Many psychiatric diagnoses are based primarily on symptom clusters rather than objective biological markers, which can lead to diagnostic overlap and uncertainty.

Major depressive disorder (MDD) is a severe affective disorder characterized by persistent low mood, anhedonia, negative self-referential thinking, and ruminative cognitive styles [4,5]. In contrast, schizophrenia (SZ) is a psychotic disorder marked by disturbances in reality testing, abnor-

mal salience attribution, motivational deficits, and altered self-processing, often manifesting as paranoid ideation and delusional beliefs [6,7]. Despite the establishment of these distinctions, differentiating SZ and MDD can be challenging, where emotional and cognitive symptoms may overlap, particularly during early-stage illness. Identifying neural markers that quantify differences in how SZ and MDD patients process diagnostically relevant emotional information could therefore enhance diagnostic precision and guide the development of interventions.

Numerous neuroimaging studies have aimed to identify structural and functional abnormalities across psychiatric disorders. However, these findings have often been inconsistent and difficult to translate into clinical practice [8]. One proposed strategy to improve reliability and clinical relevance is to integrate established psychometric instruments with neurobiological measures, thereby cross-validating subjective symptom reports with objective neural activation patterns. The combined use of functional magnetic resonance imaging (fMRI) and self-assessment scales has been suggested as a promising approach to achieve this goal [9].

In this context, Stoyanov [9] developed a translational cross-validation paradigm that integrates a clinical self-assessment scale with simultaneous fMRI data acquisition to cross-validate evaluations of psychopathology with neuroimaging techniques. In this approach, statements derived from the von Zerssen Paranoid–Depression Scale are presented as task stimuli during fMRI, enabling direct comparison of subjective symptom-related processing with corresponding neural activation patterns.

The reliability and diagnostic utility of this paradigm were tested with two studies. In the first study [10], statements from the Von Zerssen paranoid-depression questionnaire scale were used during fMRI to differentiate patients with depressive episodes (including MDD and bipolar disorder) from healthy control participants. The author reported that, compared with healthy controls, depressive patients showed increased activation in frontal, temporal, supplementary motor, precentral, and postcentral regions when processing diagnostically specific statements relative to neutral statements. In the second study [11], the same experimental paradigm was used to differentiate patients with depressive episodes (including MDD and bipolar disorder) from patients with schizophrenia. This study demonstrated diagnostic task–specific activation patterns and aberrant functional connectivity, suggesting that symptom-relevant stimuli combined with fMRI may aid in the differential diagnosis of affective and psychotic disorders.

Building on these findings, the present study aimed to replicate this paradigm in an independent Chinese cohort, focusing specifically on patients with schizophrenia and major depressive disorder. We examined neural responses in 30 patients with MDD and 27 patients with SZ during a block-design fMRI task consisting of diagnostically neutral statements, depressive-specific statements, and paranoid-specific statements. Consistent with the original study, our primary contrast of interest (paranoid-specific versus depressive-specific statements; PS > DS) was selected to isolate the relative engagement of paranoia- versus depression-related cognitive–emotional processing. This approach allowed us to assess whether SZ and MDD exhibit dissociable neural responses to diagnostically salient emotional cues and to evaluate the cross-cultural robustness of previously reported group-level activation differences.

2. Materials and Methods

2.1 Participants

We recruited 62 schizophrenia and major depressive disorder patients according to the diagnostic criteria of DSM IV-TR [12]. The assessment of the participants was performed by experienced psychiatrists using the general clinical interview [13] and the structured Mini International Neuropsychiatric Interview (M.I.N.I. 6.0) [14], as well as the Montgomery–Åsberg Depression Rating Scale (MADRS) [15], Hamilton Depression Scale (HAMD-21) [16], and the Positive and Negative Syndrome Scale (PANSS) [17]. Diagnosis was established based on the clinical interview, the presented medical documentation, and additional information from accompanying family members (in most cases). The Chinese translation of the short version of M.I.N.I. 6.0 was used to confirm the current episode (major depressive or psychotic) and the diagnosis (major depressive disorder or schizophrenia). The same instrument served to rule out comorbid disorders such as panic disorder, agoraphobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, eating disorders (anorexia and bulimia), alcohol or other substance use disorders, and dissocial personality disorder. The exclusion criteria were: under the age of 18 or over the age of 65, presence of metal implants or body grafts (e.g., pacemaker) incompatible with MRI, comorbid mental disorder as identified by the clinical interview and the M.I.N.I., (e.g., substance or alcohol use disorder, obsessive-compulsive disorder), severe somatic or neurological disease, traumatic brain injury with loss of consciousness, and none of the patients had received antipsychotic, antidepressant, or other psychotropic medications 2 weeks prior to study participation, this was done to control for the potential confounding effects of pharmacological treatment. A two-week washout period was implemented, consistent with common practices in psychopharmacological and neurobiological research. Previous work has shown that a two-week discontinuation is generally sufficient to reduce measurable effects of antidepressants and benzodiazepines on neurophysiological outcomes [18]. Furthermore, clinical studies indicate that a short-term washout of approximately two weeks can be conducted without significant symptom worsening in depressed patients, supporting its safety and feasibility [19].

From a pharmacokinetic and safety perspective, clinical guidelines often recommend washout periods of one to two weeks when discontinuing or switching psychotropic medications to avoid residual drug effects and adverse interactions [20,21], however, medication use before the two-week washout period was obtained for each patient. Anamnesis of previous episodes and treatments was further considered as a source of information to supplement the exclusion criteria. The exclusion criteria were based on DSM-TR [12]. The clinical assessments and administered scales (MADRS, HAMD-21, and PANSS) were conducted over an average of 68 minutes per participant. All participants were recruited from the inpatient department of the Sichuan Mental Health Center, Sichuan Provincial People's Hospital, Chengdu, Sichuan, China. Recruitment was conducted consecutively, and eligible patients meeting the inclusion criteria were enrolled without intentional selection bias.

The participants were scanned on a 3T Siemens MRI scanner (MAGNETOM Vida system, syngo MR XA20; Siemens Healthineers, Erlangen, Germany) at the Sichuan Mental Health Center, Sichuan Provincial People's Hospital, with different MRI sequences: high-resolution structural scan (Sag 3D T1 FSPGR sequence), with slice thickness = 1 mm, matrix = 256 × 256, TR (repetition time) = 7.2 ms, TE (echo time) = 2.3 ms, and flip angle = 12°; one resting-state functional scan (2D EPI sequence) while resting with eyes opened (slice thickness = 3 mm, slices = 36, matrix = 64 × 64, TR = 2000 ms, TE = 30 ms, flip angle = 90°, volumes = 192); one task functional scan (slice thickness = 3 mm, matrix = 64 × 64, TR = 2000 ms, TE = 30 ms, and flip angle = 90°, volumes = 318).

2.2 Paranoid-Depression fMRI Task

The paradigm was created using E-Prime software, version 3.0 (Psychology Software Tools, Inc., Pittsburgh, PA, USA) and consists of 32 s blocks with three different active conditions and one 20 s block with the rest condition (fixation cross). The stimuli were presented using the NordicNeuroLab VisualSystem HD (NordicNeuroLab AS, Bergen, Norway; model VHD-1.3). The active blocks consisted of four written statements of 8 s each, taken from the von Zerssen Paranoid-Depression Scale. There are Depression Specific blocks with the statements from the depression subscale ("I feel like I'm going crazy", "I feel melancholy and depressed", etc.) and Paranoid-Specific blocks from the paranoia subscale ("Others exert influence on me against my will", "Sometimes my body moves on its own", etc.). The Diagnostically Neutral blocks included statements from a questionnaire about general interests and likes (such as "I like running a store", "I like buying and selling stocks and bonds", etc.). The DN, DS, and PS statements used for the current work are shown in Table 1. Four possible answers ("completely true", "mostly true", "somewhat true", "not true") and the respective four response buttons (1, 2, 3, 4) were presented under each statement. The whole task incorporated four blocks of each type, alternating between the three active conditions, followed by the rest condition (DS__rest__DN__rest__PS__rest…). Participants were instructed to read the statements carefully and respond with a button press indicating their level of agreement. During the rest condition, they had to focus on the fixation cross without thinking of anything specific.

2.3 Data Preprocessing

The first five time points were discarded to remove the T1 saturation effect, leaving the final time points at 313, then followed by slice time correction, realignment, co-registration of T1 images to corresponding functional images, normalization by Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) [22], and resampling to 3 × 3 × 3 mm^3 voxels, nuisance covariates regression using Friston 24 [23], and spatial smoothing with a 6 mm full width at half maximum (FWHM) Gaussian kernel. Subjects with a maximum translation >2 mm or rotation >2° were excluded from further analysis, leaving a total of 57 subjects consisting of 30 MDD patients and 27 schizophrenia patients. All preprocessing steps were performed using the task-based data processing assistant for resting-state fMRI, advanced edition (DPARSFA), implemented in the Data Processing & Analysis for Brain Imaging (DPABI) (version 5.4, Institute of Psychology, Chinese Academy of Sciences, Beijing, China) [24].

2.4 Task fMRI Analysis

Following data preprocessing, individual participant data were analyzed at the first level using a general linear model (GLM), which involved convolving the time series with a canonical hemodynamic response function (the task conditions—diagnostically neutral, depressive-specific, and paranoid-specific were modeled by convolving the respective block onsets with a canonical hemodynamic response function). To account for potential movement artifacts, the six rigid-body motion correction parameters were included as covariates of no interest in the model. Individual T-contrasts were then computed to compare the paranoid-specific and depressive-specific conditions. The resulting contrast maps for each participant were subsequently entered into a second-level random-effects model in Statistical Parametric Mapping (SPM12) (Wellcome Trust Centre for Neuroimaging, London, UK, https://www.fil.ion.ucl.ac.uk/spm/). This analysis aimed to identify significant differences between the schizophrenia and depression patient groups, performing comparisons for both "schizophrenia > depression" and "depression > schizophrenia". Statistical significance was established at $p < 0.05$ after family-wise error (FWE) correction, utilizing an uncorrected cluster-forming threshold of $p < 0.001$.

Also, a second-level mixed-effects ANOVA was performed to examine the effects of diagnostic group and experimental condition on brain activation. The between-

Table 1. List of diagnostically neutral, depressive-specific, and paranoid-specific statements used for the fMRI task paradigm.

Diagnostically neutral (DN)	Depressive-specific (DS)	Paranoid-specific (PS)
I like making kitchen cabinets.	I am more sensitive to criticism than before.	Others exert influence on me against my will.
I like to stack bricks or tiles.	I cry easily.	I'm afraid of losing my mind.
I like developing a new kind of medicine.	Lately, I have been more anxious and fearful.	Sometimes my body moves on its own.
I like studying ways to reduce water pollution.	I feel melancholy and depressed.	People are wrong when they think I am sick.
I like to write books or plays.	Sometimes I feel tired.	Someone wants to kill me.
I like playing a musical instrument.	I don't understand what I read as well as I used to.	Someone wants to destroy my mind.
I like teaching a person new habits.	I want to take my life.	The others are constantly watching and controlling me.
I like helping people with personal and emotional problems.	I love all kinds of games and entertainment for my free time.	I have the feeling that I am being affected by electric current, rays, or hypnosis.
I like buying and selling stocks and bonds.	I feel especially bad in the mornings.	Comments are made about all my thoughts and actions.
I like running a store.	I feel like I'm going crazy.	I am noticing strange changes in my body.
I like to make a spreadsheet using computer software.	I no longer have really close relationships with other people.	People envy my knowledge, discoveries, and special experiences.
I like correcting documents and forms.	I am constantly afraid that I might say or do something wrong.	I have strange experiences such as visions, inspirations, and the like.
I like to repair household appliances.	I am much less interested in my love life than I used to be.	Sometimes I feel superhuman and invincible strength within me.
I like to raise fish in a hatchery.	I often feel just miserable.	There are people who try to steal my thoughts and ideas.
I like doing chemical experiments.	No matter how hard I try, I can't think straight.	When I think of something, others already know what it is.
I like to study the motion of the planets.	I don't have any feelings anymore.	Sometimes I make up my own new words that others don't always understand.

fMRI, functional magnetic resonance imaging.

subject factor was Group, comprising two levels: patients with schizophrenia (SZ; n = 27) and patients with major depressive disorder (MDD; n = 30). The within-subject factor was Condition, comprising two levels corresponding to the task conditions (PS and DS). For each participant, contrast images representing the PS and DS conditions from the first-level analysis were entered into the second-level model. The factorial design, therefore, included four cells: SZ-PS, SZ-DS, MDD-PS, and MDD-DS. The subject was modeled as a random factor to account for repeated measurements across conditions. This model enabled simultaneous testing of the main effect of group, the main effect of condition, and the group × condition interaction across the whole brain. Group differences independent of task condition were assessed using contrasts comparing the average activation of the SZ and MDD groups. Condition effects were examined by contrasting PS and DS conditions across both groups. The interaction contrast tested whether the difference between PS and DS conditions differed between the two diagnostic groups. Statistical significance was established at $p < 0.05$ after FWE correction, utilizing an uncorrected cluster-forming threshold of $p < 0.001$. The potential confounding effects of age, sex, medication use, education, and body mass index (BMI) were minimized by regressing them out as covariates of no interest in the design matrix. When examined individually, age, sex, medication use and BMI did not meaningfully alter the results. However, when included simultaneously, these covariates produced modest changes in the number of statistically significant regions, likely because their combined effect accounted for additional inter-individual variability within the sample. Importantly, the overall spatial pattern of findings remained largely unchanged following covariate adjustment, supporting the robustness of the results and suggesting that the observed group differences were not primarily driven by these potential confounding factors. All analyses were done using MATLAB R2018a (MathWorks, Inc., Natick, MA, USA).

2.5 Post hoc Power Analysis

To determine whether the study had enough power to detect a significant effect. A post hoc power analysis was conducted based on the observed t-values for the significant regions (after covariate adjustment) and group sizes (30 MDD, 27 SZ). We first calculated the standardized effect sizes (Cohen's d) and then determined the power of a

Table 2. Clinical and demographic characteristics.

Variable	MDD = 30	SZ = 27	*p* value
Age	29 ± 10.18	34.22 ± 12.38	0.090
Sex (F/M)	19/11	16/11	0.750
BMI	22.26 ± 3.79	21.98 ± 3.33	0.680
Educational Attainment[a]	3.53 ± 0.86	3.11 ± 1.09	0.110
MADRS	27.50 ± 12.44	10.44 ± 10.22	<0.001
PANSS TOTAL	53.77 ± 30.00	91.37 ± 29.90	<0.001
PANSS Positive	10.77 ± 7.70	24.41 ± 9.61	<0.001
PANSS Negative	11.73 ± 9.25	23.41 ± 10.87	<0.001
PANSS General	31.27 ± 15.83	43.56 ± 14.18	<0.010

MDD, major depressive disorder; SZ, schizophrenia; F, female; M, male; BMI, body mass index; MADRS, Montgomery–Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale.

[a] Educational Attainment was coded as a categorical variable: 1 = Primary school and below; 2 = Junior high school; 3 = High school; 4 = Associate degree and above.

two-sample *t*-test based on these effect sizes, the sample size, and a conventional significance level ($\alpha = 0.05$, two-sided).

3. Results

3.1 Demographic Results

A total of 57 participants, comprising 30 MDD patients and 27 SZ patients, were included in the study after preprocessing. No significant differences in age ($p = 0.090$), sex ($p = 0.750$), BMI ($p = 0.680$), or educational attainment ($p = 0.110$) were found between SZ and MDD patients. As expected, MDD had a significantly higher MADRS score than SZ, whereas SZ exhibited significantly higher PANSS total and subscale scores than MDD. Detailed information about the subjects is presented in Table 2.

3.2 fMRI Results

Comparing schizophrenia and major depressive disorder patients (SZ > MDD) using a two-sample *t*-test on the PS versus DS contrast yielded three significant clusters after multiple comparison correction (Table 3). The first cluster was located in the left supplementary motor area, extending to the right supplementary motor area and left middle cingulate gyrus, with a cluster size of 166 voxels, a level of significance $p < 0.001$, and peak Montreal Neurological Institute (MNI) coordinates [–6, –12, 63]. The second cluster was located in the right precentral gyrus, extending to the right superior frontal gyrus and right frontal middle gyrus, with a cluster size of 100 voxels, a level of significance $p = 0.006$, and peak MNI coordinates [36 –12 60]. The third cluster was located in the left precuneus and extended to the left parietal gyrus, with a cluster size of 84 voxels, a level of significance $p = 0.013$, and peak MNI coordinates [–14 –60 63]. After adjusting for age, sex, BMI, medication use, and education, only the first and second clusters remained significant between the two groups (Fig. 1). The opposite comparison (MDD > SZ) did not yield significant results.

From the second-level mixed-effects ANOVA analysis, we did not find any significant main effect of group, even with an uncorrected $p = 0.001$. However, the analysis revealed a main effect of Condition (PS versus DS) (Fig. 2 and Table 4), reflecting task-related modulation of neural activity across both diagnostic groups. Three clusters were found showing a significant main effect of condition. The first cluster was located in the left precuneus, extending to the right precuneus and left calcarine, with a cluster size of 560 voxels, a significance $p < 0.001$, and peak MNI coordinates [–12 –66 33]. The second cluster was located in the left middle frontal gyrus and extended to the left superior frontal gyrus, with a cluster size of 239 voxels, a significance $p < 0.001$, and peak MNI coordinates [–24 24 45]. The third cluster was located in the left hippocampus, extending to the left fusiform and the left parahippocampal gyrus, with a cluster size of 128 voxels, a significance $p < 0.010$, and peak MNI coordinates [–36 –18 –18]. Importantly, a significant group × condition interaction was identified in several brain regions, indicating that the neural response to the PS and DS conditions differed between the SZ and MDD groups. The interaction analysis revealed 4 significant clusters similar to the results from the two-sample *t*-test between SZ and MDD on the PS versus DS contrast (Fig. 3 and Table 5). The first cluster was located in the right supplementary motor area, extending to the left middle cingulum and the left supplementary motor area, with a cluster size of 210 voxels, a significance $p < 0.001$, and peak MNI coordinates [3 –3 51]. The second cluster was located in the right precentral gyrus and extended to the right superior frontal gyrus, with a cluster size of 129 voxels, a significance $p < 0.010$, and peak MNI coordinates [36 –12 60]. The third cluster was located in the right superior temporal gyrus, with a cluster size of 87 voxels, a significance *p*

Table 3. Brain regions showing significant differences between schizophrenia patients and major depressive disorder patients (schizophrenia > depression for the PS versus DS contrast).

Brain region	Peak MNI coordinates	T value	CS	*p* value
Covariate adjusted				
Supp_Motor_Area_L	–6 –12 63	4.97	139	0.001
Supp_Motor_Area_R	3 –3 51	4.70	139	0.001
Cingulum_Mid_L	–6 –9 39	4.48	139	0.001
Precentral_R	36 –12 60	4.48	93	0.009
Frontal_Sup_R	21 –6 63	4.43	93	0.009
Covariate unadjusted				
Supp_Motor_Area_L	–6 –12 63	5.18	166	<0.001
Supp_Motor_Area_R	3 –3 51	5.07	166	<0.001
Cingulum_Mid_L	–6 –9 39	4.63	166	<0.001
Precentral_R	36 –12 60	4.62	100	0.006
Frontal_Sup_R	21 –6 63	4.26	100	0.006
Frontal_Mid_R	27 –3 54	3.98	100	0.006
Precuneus_L	–14 –60 63	4.77	84	0.013
Parietal_Sup_L	–21 –54 57	3.75	84	0.013
Parietal_Sup_L	–27 –54 66	3.65	84	0.013

MNI, Montreal Neurological Institute; CS, cluster size; R, right; L, left; Supp, supplementary; PS, paranoid-specific; DS, depressive-specific; Mid, middle.

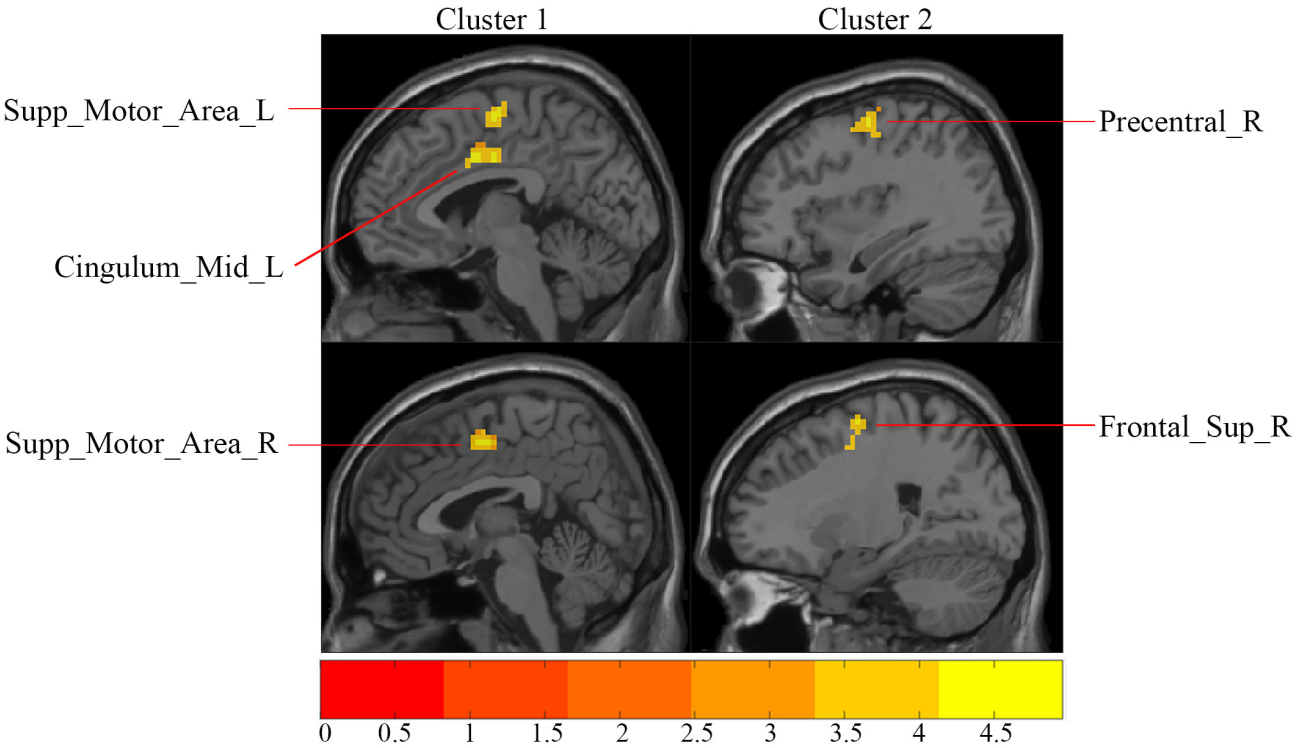

Fig. 1. Two-sample *t*-test between schizophrenia and depression patients (schizophrenia > depression) on the PS versus DS contrast. FWE corrected, $p < 0.05$. FWE, family-wise error. n = 30 MDD, n = 27 SZ.

< 0.010, and peak MNI coordinates [57 –30 12]. The fourth cluster was located in the left middle frontal gyrus, with a cluster size of 97 voxels, a significance $p < 0.010$, and peak MNI coordinates [–36 39 39].

3.3 Post-hoc Power Analysis Results

Using the provided summary statistics and a sample size of 57 (30 MDD and 27 SZ), the corresponding effect sizes were large (Cohen's d ≈ 1.20–1.34), yielding statistical power estimates exceeding 0.99 for all reported regions

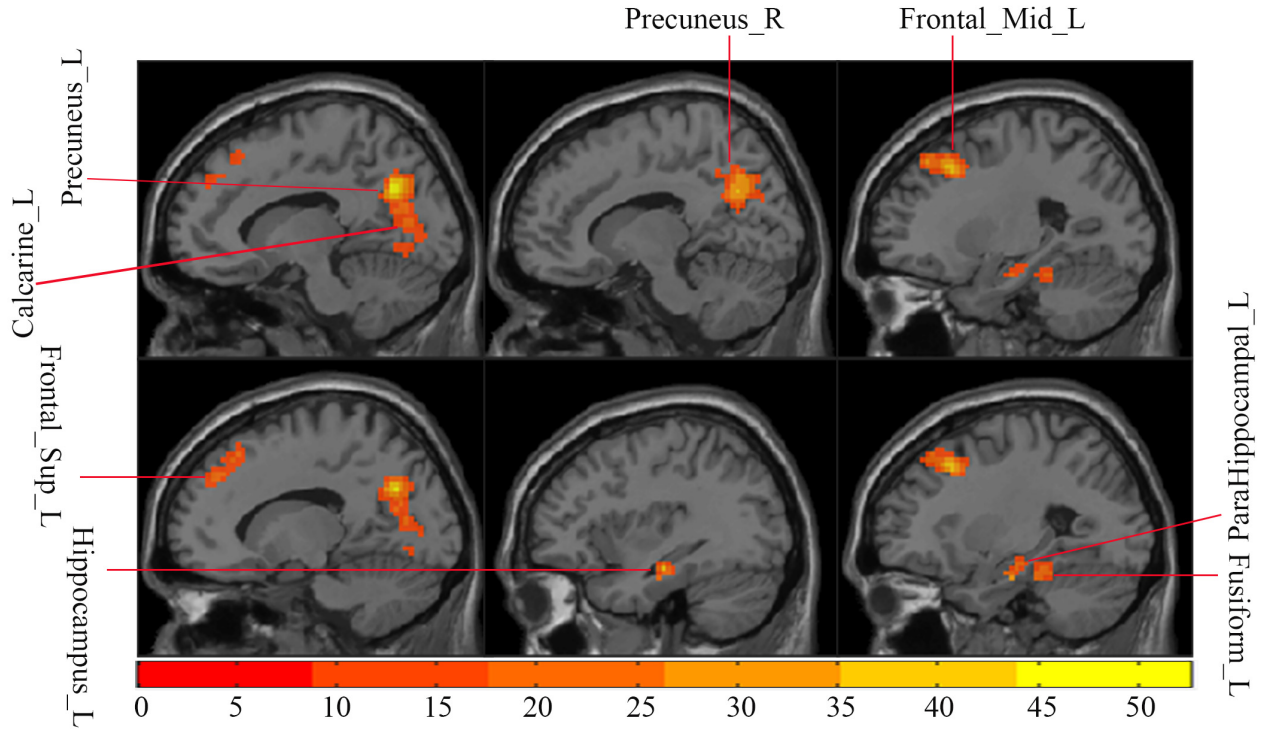

Fig. 2. Brain regions showing the main effect of Condition (PS versus DS). FWE corrected, $p < 0.05$. n = 30 MDD, n = 27 SZ.

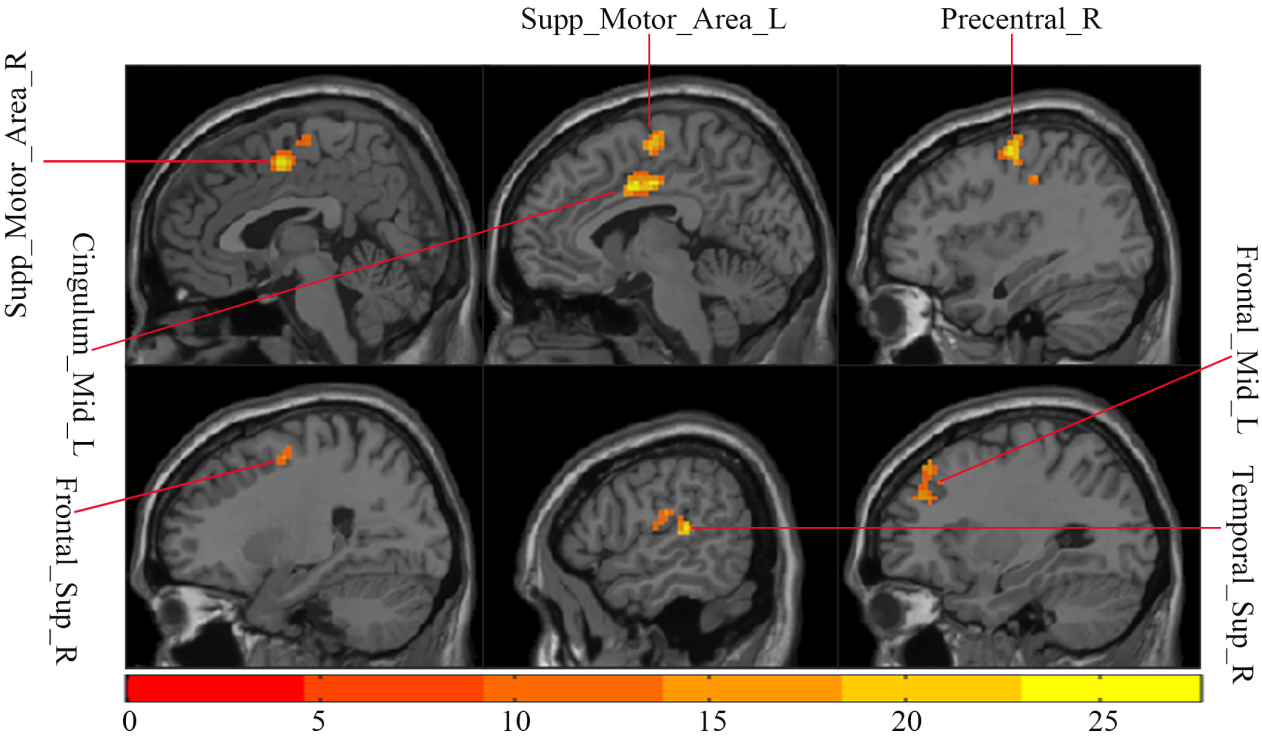

Fig. 3. Brain regions showing significant group × condition interaction. FWE corrected, $p < 0.05$. n = 30 MDD, n = 27 SZ.

at α = 0.05 (two-tailed). This indicates that the study was sufficiently powered to detect the observed group differences.

4. Discussion

The current work explored disorder-specific neural responses during the processing of paranoid-specific and depression-specific stimuli in schizophrenia and major de-

Table 4. Details of brain regions showing a significant main effect of Condition (PS versus DS).

Brain region	Peak MNI coordinates	F value	CS	*p* value
Precuneus_L	–12 –66 33	52.73	560	<0.001
Precuneus_R	12 –63 30	36.64	560	<0.001
Calcarine_L	–12 –72 12	19.75	560	<0.001
Frontal_Mid_L	–24 24 45	36.48	239	<0.001
Frontal_Sup_L	–21 36 48	28.69	239	<0.001
Hippocampus_L	–36 –18 –18	35.77	128	<0.010
Fusiform_L	–30 –33 –18	29.95	128	<0.010
ParaHippocampal_L	–27 –15 –24	26.78	128	<0.010

Table 5. Details of brain regions showing a significant group × condition interaction.

Brain region	Peak MNI coordinates	F value	CS	*p* value
Supp_Motor_Area_R	3 –3 51	27.58	210	<0.001
Cingulum_Mid_L	–6 3 36	26.84	210	<0.001
Supp_Motor_Area_L	–8 –9 64	20.89	210	<0.001
Precentral_R	36 –12 60	26.96	129	<0.010
Frontal_Sup_R	24 –3 54	15.57	129	<0.010
Temporal_Sup_R	57 –30 12	25.33	87	<0.010
Temporal_Sup_R	63 –15 0	17.27	87	<0.010
Frontal_Mid_L	–36 39 39	18.06	97	<0.010
Frontal_Mid_L	–27 36 48	17.85	97	<0.010

pressive disorder. Our results revealed a distinct pattern of increased activation in SZ relative to MDD across the bilateral supplementary motor area, the left middle cingulate cortex, the right precentral gyrus, and the right superior frontal gyrus. These findings indicate that paranoia-relevant cognitive–emotional processing engages a motor–premotor–cingulate network more strongly in SZ than in MDD, providing insight into disorder-specific neural mechanisms underlying self-referential and threat-related appraisal.

The supplementary motor area and precentral gyrus are crucial for voluntary motor control, motor imagery, and the coupling of motor and cognitive processes [25]. Aside from motor functions, these regions are also involved in internal cognitive effort and emotional embodiment, especially during tasks involving affective content or self-referential processing [7,26]. This interpretation aligns with predictive-coding and aberrant-salience accounts of psychosis, which propose that ambiguous or self-relevant stimuli receive excessive weight, leading to disproportionate affective or behavioral responses [6,27,28]. By its nature, paranoid-related content carries potential threat, ambiguity, and self-relevance, features that may induce exaggerated preparatory responses in neural circuits that assess and prepare for possible danger. Previous work further supports this work: both structural and perfusion abnormalities in the supplementary motor area have been reported in SZ, including SMA hyperperfusion in catatonia-spectrum motor dysfunction [25,26], and meta-analytic evidence has demonstrated disrupted connectivity in the precentral and sensorimotor cortices in SZ [29]. The increased brain activity of these regions observed in SZ patients suggests that individuals with SZ may exhibit heightened action-readiness or motor simulation when processing paranoia-relevant content.

Alternatively, the supplementary motor area and precentral gyrus are functionally heterogeneous and are also implicated in cognitive control, response selection, and conflict monitoring [25,30]. From this perspective, the observed activation may alternatively reflect increased cognitive effort or conflict processing when patients with schizophrenia interpret paranoid content. Moreover, premotor and motor cortices have been associated with embodied emotional processing, suggesting that affective stimuli may engage action-related representations [31]. Therefore, the increased SMA/precentral activation in schizophrenia may reflect a combination of motor simulation, cognitive control demands, and emotional embodiment processes. Given the absence of direct behavioral or effort-related measures, these interpretations remain speculative and should be examined in future studies.

The superior frontal gyrus, a part of the dorsomedial prefrontal cortex, is involved in introspection, emotion regulation, and self-evaluation [7]. Heightened brain activity of this region in schizophrenia patients may imply an increased association of cognitive–emotional control processes when processing paranoid-specific content. The middle cingulate cortex is implicated in multiple functions, including self-referential processing, threat appraisal, and action selection. In the context of paranoid stimuli, these functions are likely to operate in an integrated manner. Paranoid content is inherently self-relevant and often

involves perceived social threat, which may simultaneously engage self-referential evaluation and threat appraisal processes. Neuroimaging research has shown that the MCC plays a central role in integrating affective salience with action-related responses, particularly under conditions of perceived threat or conflict [32,33]. From this perspective, the increased MCC activation observed during paranoid stimulus processing may reflect the combined influence of heightened self-relevance, threat evaluation, and preparation for defensive or adaptive responses, rather than a single isolated function. The MCC also integrates cognitive control with affective salience and motor readiness [32,34], and is considered part of a parietal–frontal integrative pathway, connecting the precuneus/superior parietal lobe with the medial superior frontal gyrus [35]. Disruption within this tract may lead to distortions in the processing of self-related information, resulting in fragmented, overly salient, or hyper-personalized content—mechanisms that could plausibly contribute to the emergence of paranoid ideation. Although involvement of this pathway has also been observed in MDD, its role appears to be more focused on maladaptive self-focused thought, such as rumination, rather than impairments in reality testing [36].

These findings resonate with theories of disrupted self-referential processing in SZ. Disturbances in the interpretation of internally generated thoughts and intentions are well documented in psychosis, including altered monitoring of internal signals and misattribution of agency [37,38,39]. When confronted with PS stimuli, SZ patients may therefore engage self-referential systems more intensively, leading to stronger downstream recruitment of motor–premotor regions. This exaggerated coupling may reflect a tendency for self-relevant threat cues to evoke an internal simulation of potential actions, even in the absence of overt behavior.

Another hypothesis can be formulated by considering categorical differences in how the stimuli are processed. Although both SZ and MDD patients performed the task with paranoid and depressive statements, a potential interpretation of their processing biases could be considered. Phenomenologically, when a SZ patient reads paranoid statements, they perceive them differently from others. A similar thought process could be used with MDD; hence, while SZ patients would be externalizing what others would do to them (paranoid statements), depressive patients would potentially be internalizing depressive stimuli (such as “I’m worthless”). Both of these are related to default mode network (DMN) activations, commonly found in both disorders. While the response to such stimuli in MDD would be emotional, in SZ, the bias toward external threat attribution would create a differential pattern (activations) characterized by agency misattribution and the intrusion of referential thinking. This depiction is consistent with the middle cingulum’s role in mentalization and agency-monitoring subnetworks (including the precuneus and the medial superior frontal gyrus) [40], which are essential for interpreting others’ intentions, detecting social threat, and embedding events in personal narrative. This subsystem is reportedly distorted in SZ but not in MDD [41].

The second-level mixed-effects ANOVA analyses provided nuanced insights into the neural processing of diagnostic-relevant emotional stimuli. Notably, there was no significant main effect of group, even at a lenient uncorrected threshold. The absence of a significant group main effect indicates that diagnostic differences may not manifest as global activation differences**,** but rather as condition-dependent neural responses. Previous neuroimaging studies have similarly reported overlapping neural activation patterns across psychiatric disorders, with disorder-specific differences emerging primarily under particular cognitive or emotional task demands [42,43]. In contrast, a significant main effect of Condition (paranoid-specific versus depressive-specific stimuli) was observed across both groups. This effect was characterized by three prominent clusters located in the precuneus and calcarine cortex, the middle frontal gyrus extending to the superior frontal gyrus, and the hippocampus extending to the fusiform and parahippocampal gyrus, implicated in self-referential and perceptual processing [44,45]. The involvement of hippocampal structures suggests that the task conditions may engage memory or emotional contextual processing systems. These findings suggest that the type of emotional content modulates activity in regions associated with internal mentation, visual processing, and memory regardless of diagnosis.

Furthermore, the significant group × condition interaction identified indicates that the neural response to the PS and DS conditions differed between patients with schizophrenia and those with major depressive disorder. The interaction effects primarily involved regions related to motor preparation and social cognition, such as the right supplementary motor area and precentral gyrus, as well as temporal areas like the superior temporal gyrus and the dorsolateral prefrontal cortex. These findings suggest that, although both groups engage similar networks during emotional processing, the neural dynamics underlying responses to paranoia- versus depression-relevant stimuli are distinct between SZ and MDD, underscoring disorder-specific mechanisms that may contribute to differential symptom expression. Importantly, the interaction results were consistent with those obtained from the two-sample *t*-test comparing SZ and MDD on the PS versus DS contrast, providing converging evidence for diagnosis-specific differences in condition-related neural processing.

Although this study was designed to replicate an established research paradigm by Stoyanov and colleagues [11], our findings only partially replicate the specific regional activation patterns in their original work. Despite variations in the precise anatomical loci of group differences, the original and replication analyses show convergent evidence that SZ patients exhibit greater task-related activation than MDD

patients, and that this hyperactivation emerges within networks anchored in medial (midline) cortical structures, such as the medial prefrontal cortex, anterior cingulate cortex, and MCC, rather than lateral sensory areas. In the original dataset, the SZ > MDD contrast highlighted the left precuneus/posterior cingulate cortex and right superior parietal gyrus/angular gyrus—regions anchored in the DMN and neighboring frontoparietal integration zones [11]. In the replication, the schizophrenia > MDD effect shifted toward medial frontal territories, including the SMA, midcingulate cortex, right precentral, and superior frontal region, all of which are strongly interconnected with DMN hubs and play central roles in internally guided action selection and conflict monitoring. These variations likely reflect differences in sample demographics, cultural context, or methodological nuances inherent in cross-study replications. Importantly, both studies converge at the level of network-level engagement—highlighting the significance of medial cortical and motor–cingulate circuits in disorder-specific emotional processing, indicating that our findings are consistent with the broader neurofunctional framework rather than strict regional convergence. Consequently, we interpret our results as providing partial but meaningful replication, emphasizing the robustness of the overarching neural mechanisms involved while acknowledging the variability in exact anatomical loci. The results from the original and replication studies suggest that both datasets tap into the same underlying functional imbalance, expressed through slightly different subcomponents of the same broader network architecture.

The replication pattern—showing stronger activation in SZ than MDD within the SMA, midcingulate, and right precentral/SFG suggests that the diagnostic contrast may hinge on a motor–cingulate axis rather than the DMN-cognitive-control axis emphasized in the original study. Sensitivity analyses (region of interest (ROI) extraction and covariation for medication and motion) could indicate that these effects likely reflect a combination of heightened motor-related responsivity in schizophrenia and differences in how self-referential or socially salient content engages motor–cingulate regions. Thus, instead of contradicting the original directionality, the replication may capture the same broader mechanism—atypical integration of self-referential or threat-related information—expressed through motor–cingulate recruitment rather than DMN-frontoparietal interactions.

Importantly, the current study replicates the original paradigm in an independent sample from a Sichuan (Chinese) population. The convergence of findings across samples suggests that the observed neural differences are relatively robust and not restricted to a particular cultural or demographic context. This cross-sample consistency enhances the potential clinical relevance of these regions as candidate neural markers for differentiating schizophrenia and major depressive disorder. However, the present findings are based on group-level contrasts and do not yet establish diagnostic utility at the individual level. Future studies using larger, multi-site samples and predictive modeling approaches will be necessary to determine the reliability, generalizability, and clinical applicability of these neural markers.

In addition to the mechanistic interpretation, the present findings have potential implications for differential diagnosis and translational research. The observed group differences in the supplementary motor area, precentral gyrus, and middle cingulate cortex are broadly consistent with prior neuroimaging studies implicating medial frontal and cingulate regions in schizophrenia and major depressive disorder. Large transdiagnostic meta-analyses have reported overlapping but distinct abnormalities across major psychiatric disorders within these networks, supporting the existence of partially shared neural substrates alongside disorder-specific alterations [43,46].

The present study compared neural activation patterns between schizophrenia and major depressive disorder and did not include patients with bipolar disorder. Therefore, the findings cannot be directly generalized to bipolar depression. Neuroimaging research suggests that bipolar disorder shares certain neural abnormalities with both schizophrenia and unipolar depression, particularly within fronto-limbic and salience-network regions, supporting transdiagnostic models of psychiatric disorders [43,46]. At the same time, bipolar disorder also exhibits state-dependent neural alterations, especially in circuits involved in emotional regulation and reward processing, which may distinguish bipolar depression from unipolar depression [47]. As such, bipolar depression may show neural responses that are intermediate between schizophrenia and major depressive disorder, or display distinct patterns depending on mood state. Future studies including bipolar disorder across different illness phases will be important for clarifying whether the neural differences observed in the present study extend to bipolar depression or reflect disorder-specific mechanisms.

5. Limitations

Several limitations should be considered when interpreting the study findings. First, the relatively limited sample size in the present study should be considered when interpreting the stability and reproducibility of the findings. Smaller samples can increase the variability of estimated effect sizes and may reduce the reliability of statistical inferences, particularly in neuroimaging analyses where multiple comparisons and complex brain–behavior relationships are involved. Consequently, the observed effects may be more susceptible to sampling variability, and the magnitude of the reported associations may not fully generalize to broader clinical populations. In addition, limited sample sizes may reduce the ability to detect more subtle effects that could be biologically meaningful. Therefore, while the

current results provide preliminary evidence of the neural patterns associated with the studied condition, replication in larger and independent cohorts will be essential to confirm the robustness, stability, and generalizability of the reported findings. Second, the cross-sectional design of the present study limits the interpretation of the observed neural activation patterns. Specifically, it is not possible to determine whether these patterns reflect trait-like characteristics of schizophrenia and major depressive disorder or state-dependent effects associated with current symptom severity, treatment status, or illness chronicity. Longitudinal studies are required to disentangle stable neural markers from dynamic, symptom-related changes over time. Third, our study employed a cross-sectional design involving two clinical cohorts without a healthy comparison group. Incorporating a healthy control group into future case-control studies would enhance the interpretability of brain differences, enabling a clearer understanding of how these neural patterns deviate from typical functioning. Fourth, all participants were assessed within a specific clinical and cultural context, which may limit applicability to broader populations. Fifth, the present study focused primarily on group-level differences between schizophrenia and major depressive disorder. As such, associations between neural activation and symptom severity were not examined. This limits the ability to draw mechanistic conclusions regarding the relationship between regional brain activity and specific psychopathological dimensions. Future studies using larger samples and dimensional approaches to symptom assessment will be important for clarifying the links between neural activation patterns and clinical severity. Sixth, although our study identified differential neural activation patterns between schizophrenia and major depressive disorder, behavioral response patterns to depressive, paranoid, and neutral stimuli were not analyzed. Therefore, the interpretation that patients with schizophrenia may externalize paranoid stimuli while patients with depression may internalize depressive stimuli remains theoretical and is not directly supported by behavioral data from the current sample. We acknowledge that including behavioral performance would provide additional context for interpreting neural findings. As such, the absence of these analyses limits the ability to establish a direct link between neural activation differences and specific cognitive or emotional processing biases. Future studies incorporating detailed behavioral analyses will be important for clarifying the relationship between stimulus processing patterns and underlying neural mechanisms. Lastly, despite the efforts to control for potential confounding factors, residual effects of medication history and comorbidities cannot be entirely ruled out. Future studies should perform post-hoc analyses by including indices of prior medication exposure as covariates, such as treatment duration and dose equivalents. Addressing these limitations in future research will be essential to validate and extend these findings.

6. Conclusions

In sum, the present findings provide evidence that processing paranoia-related internal content preferentially engages motor–premotor–cingulate networks in SZ patients relative to MDD. Because the PS versus DS contrast isolates neural systems involved in paranoia-specific processing, the absence of MDD > SZ differences suggests that MDD patients engaged these paranoia-related statements to a lesser extent than patients with schizophrenia. This highlights the importance of disorder-specific stimulus design when investigating transdiagnostic psychiatric constructs that may arise from distinct underlying mechanisms. The absence of comparable effects in MDD further suggests that depression-related cognitive processes likely involve different neural systems that are not captured by the present contrast. More broadly, the results indicate that task condition strongly modulates neural activity across both diagnostic groups, engaging distributed networks associated with default mode processing, cognitive control, and memory systems. Although no overall diagnostic differences were observed, the significant group × condition interaction demonstrates that schizophrenia and major depressive disorder differ in how neural systems respond to specific task demands. By selectively isolating neural circuits associated with paranoia-related appraisal, the present study strengthens the methodological validity of this approach, supports mechanistic distinctions between schizophrenia and depression, and contributes to the identification of potential neurobiological markers for transdiagnostic psychiatric research. Clinically, such markers may ultimately improve diagnostic differentiation and support personalized treatment strategies by identifying disorder-specific neural targets for intervention.

Abbreviations

MDD, major depressive disorder; SZ, schizophrenia; DS, depressive-specific; PS, paranoid-specific; DN, diagnostically neutral; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; fMRI, functional magnetic resonance imaging; TR, Repetition Time; TE, Echo Time; FWHM, full width at half maximum; MNI, Montreal Neurological Institute; M.I.N.I., Mini International Neuropsychiatric Interview; L, left; R, right; Sup, superior; Mid, middle; Supp, supplementary; FWE, family-wise error; BMI, body mass index; GLM, general linear model; DARTEL, Diffeomorphic Anatomical Registration using Exponentiated Lie algebra; DPABI, Data Processing & Analysis for Brain Imaging; DMN, default mode network; MCC, middle cingulate cortex; SMA, supplementary motor area; ROI, region of interest.

Availability of Data and Materials

The data used for this study are available upon request from the corresponding authors.

Author Contributions

EA, MM, PW, CY, and YZ contributed to the study conception and design. EA, HW, MM, BKB, and SF contributed to the methodology. EA, BKB, LPL, AFC, and MM were responsible for formal analysis and investigation. EA, HW, ML, YZ, CY, and PW contributed to data acquisition. EA, LPL, and AFC drafted the original manuscript. MM acquired the funding. MM, LPL, AFC, and BKB supervised. 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 work was approved by the ethics committee of the University of Electronic Science and Technology of China (IRB Number: 30850). Each participant provided written informed consent. The study was carried out in accordance with the Declaration of Helsinki.

Acknowledgment

We want to acknowledge the doctors, nurses, and MRI staff at the Sichuan Mental Health Center of the Sichuan Provincial People's Hospital for their support during participant recruitment and scanning.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

Grammarly was used to proofread and correct grammatical errors. After using this tool, the authors conducted a comprehensive review and revision of the content as required, and assume full responsibility for the integrity and accuracy of the publication content.

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