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Differential relationships among homocysteine levels, cognitive deficits, and low-frequency fluctuation in brain activity in bipolar disorder with suicidal ideation

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Abstract

Background Suicidal ideation (SI) is a common symptom of bipolar disorder (BD). Patients with BD and suicidal ideation (BDSI) have been shown to exhibit abnormal spontaneous brain activity and homocysteine (Hcy) levels. Additionally, cognitive deficits are also considered to be a critical symptom in BD. However, the relationship among spontaneous brain activity, Hcy levels, and cognitive deficits in patients with BDSI remains unclear.

Methods A total of 74 participants were enrolled, comprising individuals with BDSI ($n=20$), BD patients without suicidal ideation (BDNSI) ($n=24$), and age-/sex-matched healthy controls (HC) ($n=30$). Each participant underwent cognitive performance assessments, and blood samples were collected to measure Hcy levels. We then calculated the amplitude of low-frequency fluctuation (ALFF) from resting-state functional magnetic resonance imaging data. Mediated-effects analysis was conducted to explore the association among these three variables.

Results Hcy levels were significantly higher in the BDNSI group than in the BDSI group ($t=2.33$, $P=0.024$). Specifically, a significant positive correlation was observed between Hcy levels and the fractional amplitude of low-frequency fluctuation (fALFF) signals in the left posterior cingulate gyrus in the BDSI group ($r=0.644$, $P=0.005$). Mediation analyses revealed that the left posterior cingulate gyrus significantly mediated the negative relationship between Hcy levels and both visual learning /verbal learning performance (95% confidence intervals for the indirect effects ranging from −0.592 to −0.069 and −0.465 to −0.042, respectively) in the BDSI group.

Conclusions Our data suggest that patients with BDSI and BDNSI may exhibit distinct Hcy-neurocognitive-brain function profiles, which could be further verified by investigating the underlying pathophysiological mechanism of BDSI.

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Keywords Cognitive deficits, Homocysteine, Low-frequency fluctuation, Suicidal ideation

Introduction

Bipolar disorder (BD) is a mental health condition characterized by recurrent manic or hypomanic episodes and severe depression [1]. It is a major public health concern, as suicide is considered one of the leading causes of death worldwide, accounting for approximately 800,000 deaths per year [2]. Individuals with BD are at an especially high risk of suicide, with an estimated 15–20% of patients succumbing to suicide [3]. Suicidal behavior exists on a continuum, ranging from suicidal ideation (SI) to suicide attempts and completed suicide [4, 5]. Intensive research focused on SI has attracted widespread attention in public health, as it can help us better understand the progression of suicidal behaviors [6].

Homocysteine (Hcy) is a sulfur-containing amino acid, partially metabolized by methionine [7]. It has been identified as a risk factor for several psychiatric disorders including depression, obsessive-compulsive disorder, schizophrenia, and Alzheimer's disease [8, 9]. A meta-analysis showed that Hcy levels are elevated in individuals with BD, during both manic episodes and periods of euthymia [10]. This suggests that peripheral Hcy may serve as a potential biomarker for BD, reflecting both trait characteristics (increased during stabilization) and state-specific changes (more pronounced during mania) [10, 11]. Furthermore, another meta-analysis identified a significant association among activated immune-inflammatory pathways, nitro-oxidative stress, and suicidal actions [12]. However, few studies have explored the relationship between Hcy levels and suicide [1]. Bai et al. reported that Hcy is not a risk factor for suicide in major depression [13]. In conclusion, outpatients with alexithymic major depressive disorder (MDD) may exhibit Hcy dysregulation linked to SI, independent of the severity of their depression [14]. However, due to inconsistent inclusion criteria and limited sample sizes across the aforementioned studies, caution is required when interpreting these findings.

Cognitive deficits are the core feature of BD and often complicate its clinical presentation. Hcy, particularly in its oxidized form, is considered to be a neurotoxic agent that can cause neuronal apoptosis and leukoaraiosis [15]. Disruptions in methylation pathways, including the methylation of DNA, neurotransmitters, and phospholipids, negatively affect cerebral tissue [16–18]. Previous studies have demonstrated a correlation between higher peripheral Hcy levels and poorer cognitive performance in patients with BD [11, 16, 19]. Recently, Osher et al. revealed that male individuals with BD exhibit worse executive function when their Hcy levels are elevated, indicating that elevated Hcy levels may significantly contribute to cognitive deficits particularly executive dysfunction in BD [20]. Furthermore, Wang et al. reported that cognitive vulnerability, together with negative life events, contribute in predicting the likelihood of developing depressive symptoms in the future [21].

Neuroimaging studies have demonstrated structural and functional changes in the brains of patients with suicidal BD [22]. However, these alterations in brain dynamics remain variable. The amplitude of low-frequency fluctuations (ALFF) is calculated by taking the average square root within the bandpass range (0.01–0.08 Hz) for each voxel after performing a fast Fourier transform, representing regional spontaneous neuronal activity [23, 24]. The fractional amplitude of low-frequency fluctuation (fALFF) is defined as the ratio of low-frequency power (0.01–0.1 Hz) to the total power across the entire frequency range [25]. Previous studies have revealed a similarly positive correlation between SI and the ALFF in the right hippocampus in bipolar depression [23, 26]. A reduction in amygdala-prefrontal functional connectivity has been associated with a higher severity of SI among suicide attempters [27]. The dynamic ALFF was found to be increased in the right temporal pole in the suicide attempters group compared to both the SI group and healthy controls, as well as in the right superior temporal gyrus and inferior temporal gyrus in the suicide attempters group compared to other groups [28]. Notably, previous research has demonstrated that in BD patients with SI, the ALFF in the left precuneus is negatively correlated with cognitive deficits [29]. A study on patients with cognitive impairment due to end-stage renal disease found that in these patients, higher cognitive performance scores, lower Hcy levels, and higher whole-brain ALFF coupling indexes are associated [30]. These findings suggest that significant changes in neural activity and Hcy levels may underlie suicidal ideation in BD and are closely related to cognitive impairment.

Despite these insights, the interplay between Hcy levels, ALFF, and cognitive impairment in patients with BD and SI remains underexplored. This study aims to investigate their relationships using neuroimaging and blood Hcy analysis, providing evidence for future research.We hypothesized that (1) Hcy levels differ between the bipolar disorder with suicidal ideation (BDSI) and bipolar disorder without suicidal ideation (BDNSI) groups; (2) Significant relationships are existent among Hcy, ALFF/fALFF, and cognitive deficits in the BDSI group; and (3) There is a mediating effect between ALFF/fALFF, Hcy levels, and cognitive impairment.

Methods

Study participants

A total of 44 individuals with BD were enrolled from the inpatient and outpatient units at the Affiliated Brain Hospital of Guangzhou Medical University. Additionally, 30 sex- and age-matched healthy controls from the Guangzhou community were included between June 2020 and September 2021. The Ethics Committee at Affiliated Brain Hospital of Guangzhou Medical University granted approval for this study, and the research was carried out following the latest revision of the Declaration of Helsinki (2013). All participants signed informed consent forms before their engagement in the research.

This is a cross-sectional study. We enrolled patients based on the following criteria: (1) individuals aged 18–65 years; (2) individuals with BD meeting the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR); (3) patients with BD in remission, defined by a 17-item Hamilton Rating Scale (HAMD-17) [31]score below 7 and a Young Mania Rating Scale (YMRS) [32] score below 5 over four consecutive visits; (4) individuals showing no significant manic or depressive symptoms at the time of the study; and (5) individuals who were stable on any commercially available atypical or typical antipsychotic medications, with up to two antipsychotics prescribed, and all psychiatric medications were stable for up to 2 weeks, with no increase in medication dosage in the past 2 weeks.

The exclusion criteria were as follows: (1) comorbid psychiatric disorders; (2) serious physical illnesses; (3) a history of epilepsy, intellectual disability, brain trauma, and other relevant medical conditions; (4) having undergone electroconvulsive therapy in the past 6 months; and (5) being pregnant or had been receiving steroidal or nonsteroidal anti-inflammatory drug treatment.

This study was approved by the Institutional Research Committee of the Brain Hospital of Guangzhou Medical University, and written informed consent was obtained from all participants.

Assessment of clinical symptoms

The HAMD-17 and YMRS were used to evaluate the severity of depressive and manic symptoms in patients with BD over the past week [33]. In the present study, SI was defined as a score of ≥ 3 on item 3 of the HAMD-17, and the history of SI was assessed using specific questions from the HAMD-17 (e.g., "Have you ever had suicidal thoughts?" and "Over the past year, have you thought that you would be better off dead?") [28]. Consequently, patients with BD were divided into two groups: the BDSI ($n = 20$) and BDNSI ($n = 24$) groups.

The MATRICS Consensus Cognitive Battery (MCCB) was employed to evaluate cognitive deficits. Five dimensions from the MCCB were selected for this study based on previous research [34, 35], including the speed of the processing domain score (SoP), working memory (WM), attention/vigilance (AV), visual learning (VisL), and verbal learning (VrbL). The results of each of these scales were reported as T-scores. All assessments were conducted by professionally trained psychiatrists and postgraduate students, who attended a training session to ensure consistency. Furthermore, the inter-rater correlation coefficient was > 0.8 based on repeated evaluations.

Peripheral inflammatory Hcy assays

The enzyme cycle method was utilized to measure fasting plasma Hcy concentrations. A research assistant, blinded to the clinical outcomes and neuroimaging results of the participants, analyzed all samples using an automated tester (AU5800 tester, Beckman Coulter, Brea, CA, USA) [36, 37]. Each sample was analyzed in triplicate.

Image acquisition and analyses

Magnetic Resonance Imaging (MRI) was conducted within a day of the clinical evaluation. The imaging data were captured using a 3.0 Tesla Philips Achieva scanner with an 8-channel head coil designed for perception. Subjects were advised to keep their eyes closed and to limit movement of the head throughout the scanning procedure. Functional MRI data collection was performed using an echo-planar imaging sequence with the following specifications: echo time (TE) = 30 ms; acquisition time = 2000 ms; repetition time (TR) = 2000 ms; field of view = 210 mm × 210 mm; spatial resolution (SR) = 3.4 × 3.4 × 4 mm; flip angle (FA) = 90 degrees; matrix size 64 × 64 × 33. T1-weighted gradient-echo images were acquired with the following parameters: TR = 8.2 ms; FA = 7°; TE = 3.7 ms; SR = 1 × 1 × 1 mm; matrix size 256 × 256 × 188 [29].

Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing and Analysis for Brain Imaging (DPABI V6.1, http://rfmri.org/dpabi) software were used for preprocessing the rs-fMRI images [38]. The preprocessing steps included: (1) removal of the first ten time points; (2) slice timing correction; (3) head motion correction; (4) image normalization and segmentation based on T1-weighted image unification, resampling to a size of 3 × 3 × 3 mm solution; (5) regression of head motion (6 rigid-body motion parameters), gray matter, white matter, cerebrospinal fluid, and global signals from fMRI data; (6) spatial smoothing with a 6 × 6 × 6 mm Gaussian kernel (full width at half maximum); (7) detrending and elimination of the linear trends in the scanning process; and (8) bandpass filtering (0.01–0.08 Hz). Participants with head movement > 0.3 mm were excluded from the analysis [39].

Using the preprocessed images, we calculated ALFF and fALFF [40]. The time series of all voxels in the brain

are converted to the frequency domain using the Fast Fourier Transform (FFT), and the average amplitude within the bandwidth of 0.01–0.08 Hz is calculated to obtain the ALFF value. Furthermore, the sum of amplitudes within the low-frequency bandwidth is divided by the total amplitude across the entire frequency band to derive the fALFF. To mitigate the influence of the original BOLD signal, both ALFF and fALFF are normalized to the mean ALFF and fALFF values across the entire brain.

Statistical analyses

Between-group differences in demographic and clinical characteristics of the three groups were evaluated using analysis of variance, two-sample t-tests, or chi-square tests. If the ANOVA shows a significant difference, post-hoc comparisons are performed using the Bonferroni method. In performing the above statistical analyses, normality and variance chi-square of the data have been tested to ensure compliance with the prerequisites of the parametric approach. To compare group differences in ALFF and fALFF across the three groups while controlling for age and head movement, we performed a one-way analysis of covariance using voxel-based analysis. Group-level multiple comparisons were corrected using the Bonferroni method, and cluster-level multiple comparisons were corrected using the Gaussian random field method, with thresholds set at a voxel-level P value < 0.001 and cluster-level P value < 0.01. In this study, $p < 0.05$ was considered significant.

To further explore the relationships among rs-fMRI measurements, Hcy levels, and cognitive function in the BDSI and BDNSI groups, we first extracted values from regions showing significant group differences in the previous analysis. We then conducted partial correlation analyses between these values and the five-dimensional MCCB scores for the three groups, adjusting for age and head movement as covariates. Finally, to test the hypothesis that brain function mediates the relationship between Hcy levels and cognitive function, the SPSS-based PROCESS macro [41] was used to perform mediation and moderation analyses. The macro employs bootstrapping, a nonparametric method that does not require inherent assumptions about data distribution.

Results

Demographic and clinical characteristics

Basic information on healthy controls, individuals with BDSI, and those with BDNSI is presented in Table 1. Significant differences were observed in years of education ($F = 7.80$, $P < 0.001$), but not in age or sex. After controlling for education, no significant differences were found in the scores of the five MCCB dimensions among the three groups ($P > 0.05$). Among the participants with BD, the BDSI group had significantly higher HAMD scores than the BDNSI group ($t = -3.69$, $P<0.01$); however, no between-group differences were observed in the YMRS scores. Figure 1 shows that the Hcy levels were significantly higher in the BDNSI group than in the BDSI group ($t=2.3$, $P=0.024$).

Intergroup differences in local brain function

We identified five regions with significantly different brain function indicator values across the three groups (Fig. 2). Compared to the healthy controls (HC) group, the BDNSI group showed decreased ALFF values in the right precuneus and decreased fALFF values in the right middle frontal gyrus and left posterior cingulate gyrus ($P < 0.05$). In contrast, the BDSI group showed increased

Table 1 Sample characteristics of the control participants and participants with suicidal ideation or no suicidal ideation in bipolar depression

Demographic	BDSI ($n=20$)		BDNSI ($n=24$)		HC ($n=30$)		$F/\chi^2/t$	P
	Mean	SD	Mean	SD	Mean	SD		
Age (year)	31.20	8.38	28.25	7.26	28.00	9.72	0.94[a]	0.40
Sex (female/male)	18/2		14/10		22/8		5.55[b]	0.62
Education (year)	13.00	3.78	12.88	2.94	**15.63[d]**	**2.06**	0.78[a]	**< 0.001**
HAMD scores	6.45	6.04	1.62	1.95	-	-	-3.69[c]	**< 0.01**
YMRS scores	1.75	4.45	0.38	0.77	-	-	-1.37[c]	0.19
MCCB								
SoP	46.60	17.83	41.75	15.90	46.13	8.47	0.87[a]	0.42
AV	47.55	11.09	46.04	13.46	45.93	10.82	0.13[a]	0.88
WM	45.55	9.52	44.67	15.35	46.97	10.25	0.25[a]	0.25
VrbL	45.05	12.76	46.17	15.51	42.17	11.36	0.66[a]	0.66
VisL	48.20	15.59	49.79	7.41	46.63	9.67	0.33[a]	0.72

[a] One-way ANOVA; [b] Chi-square test; [c] Two-sample t tests; [d] Post-hoc tests, the results showed significant education differences only between HC and BDNSI, and between HC and BDSI (Bonferroni method)

Abbreviations: BDSI, bipolar disorder with suicidal ideation; BDNSI, bipolar disorder with no suicidal ideation; HC, healthy controls; HAMD, 17-item Hamilton Depression Scale; YMRS, Young Mania Rating Scale; MCCB, the MATRICS Consensus Cognitive Battery; SoP, speed of processing; AV, attention/vigilance; WM, working memory; VrbL, verbal learning; VisL, visual learning

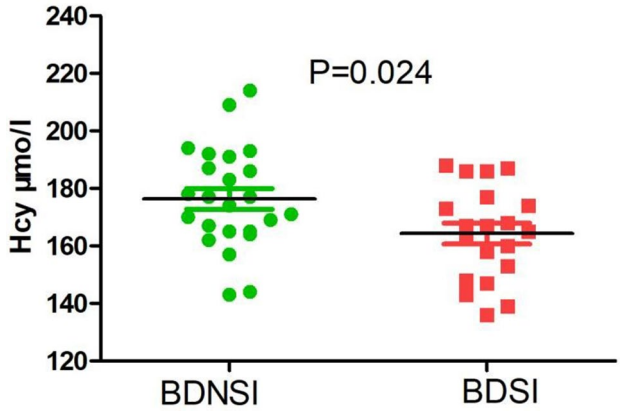

Fig. 1 Group differences in homocysteine (Hcy) levels between bipolar disorder with suicidal ideation (BDSI) and bipolar disorder with no suicidal ideation (BDNSI) groups. Green dots indicate the individuals in the BDNSI group and red dots are those in the BDSI group

ALFF values in the right posterior cingulate gyrus and left precuneus compared to the HC group. Additionally, a significant decrease in the fALFF values in the left superior frontal gyrus was observed in the BDNSI group ($P < 0.05$) but not in the BDSI group ($P > 0.05$).

Relationships between peripheral Hcy levels and cognitive deficits in BDSI and BDNSI

As demonstrated in Table 2, the partial correlation analysis revealed a negative relationship between Hcy and attention/vigilance (r= −0.506, $P = 0.038$), verbal learning (r= −0.566, P=0.018), and visual learning (r= −0.556, P=0.020) dimensions in the BDSI group after controlling for age, sex, and education. Moreover, peripheral Hcy levels were significantly and positively associated with the fALFF in the left posterior cingulate gyrus (r=0.644, P=0.005). However, no significant differences were found between the ALFF/fALFF and any of the five MCCB dimensions in the BDNSI group.

We explored whether the significant association between Hcy levels and cognitive deficits was mediated by the posterior cingulate gyrus. As shown in Fig. 3, the mediation analysis showed that the left posterior cingulate gyrus mediated the negative relationship between Hcy and both the visual learning and verbal learning scores (indirect 95% Confidence Interval (CI)= −0.592 to −0.069 and −0.465 to −0.042, respectively). After accounting for significant negative indirect mediating effects, the remaining direct effects became non-significant for the BDSI group (direct 95% CI = −0.565 to 0.258 and −0.470 to 0.215, respectively). Decomposition of the effects revealed a positive association between the left posterior cingulate gyrus and Hcy levels (T=2.60, $P = 0.018$, 95% CI=0.006 to 0.060), and a significant negative association between the left posterior cingulate gyrus and both visual learning (T= −2.96, P=0.009, 95% CI= −15.508 to −2.592) and verbal learning scores (T= −2.84, P=0.011, 95% CI = −12.608 to −1.851) in the BDSI group.

Discussion

To the best of our knowledge, this study is the first to reveal a distinct relationship among peripheral Hcy levels, abnormal brain function, and cognitive deficits in individuals with BDSI. The findings indicated that (1) Hcy levels were significantly different between the BDSI and BDNSI groups; (2) a significant relationship exists among Hcy, cognitive deficits, and fALFF signals in the left posterior cingulate gyrus in BDSI; and (3) the left posterior cingulate gyrus mediated the Hcy- visual learning and verbal learning relationship in BDSI.

Relationship between Hcy and BD

Consistent with our first hypothesis, we observed significant differences between the BDSI and BDNSI groups. Hcy is a sensitive marker of chronic inflammation, neuroapoptosis, and oxidative stress induction, which are disorders associated with BD [10]. A moderate increase in Hcy plasma levels reflects an underlying cellular stress phenomenon [42]. Previous studies suggest that Hcy is a consequence of both generic and environmental stressors, further exerting a deleterious effect on specific brain areas and contributing to the development of stress-induced psychiatric disorders such as BD [43, 44]. Our findings align with those of previous studies showing that elevated Hcy levels are significantly associated with increased suicide severity [1]. Emerging evidence indicates that the initial inflammation may serve as a protective response to mitigate adverse effects; however, prolonged inflammatory imbalances can exacerbate the severity of symptoms and mood episodes [45, 46].

Our findings suggest that the slightly higher mean Hcy levels in the BDSI group than in the BDNSI group may reflect a mild inflammatory condition that could have a protective effect against non-suicidal ideation in patients with BD. The biological mechanisms linking inflammation and suicidal behaviors require further investigation. Inflammatory cytokines can affect neural circuits in specific brain regions associated with suicidality, such as the basal ganglia, anterior cingulate cortex, and prefrontal cortex [47]. Additionally, stressors and constitutional factors associated with suicidal behaviors may interact with the immune system, resulting in elevated levels of inflammatory markers in vulnerable individuals [48].

Relationship among Hcy, ALFF/fALFF, and cognitive deficits in individuals with BDSI

This study is the first to investigate the relationship among Hcy, AFF/fALFF, and the posterior cingulate gyrus in the brains of individuals with BD. Regarding our

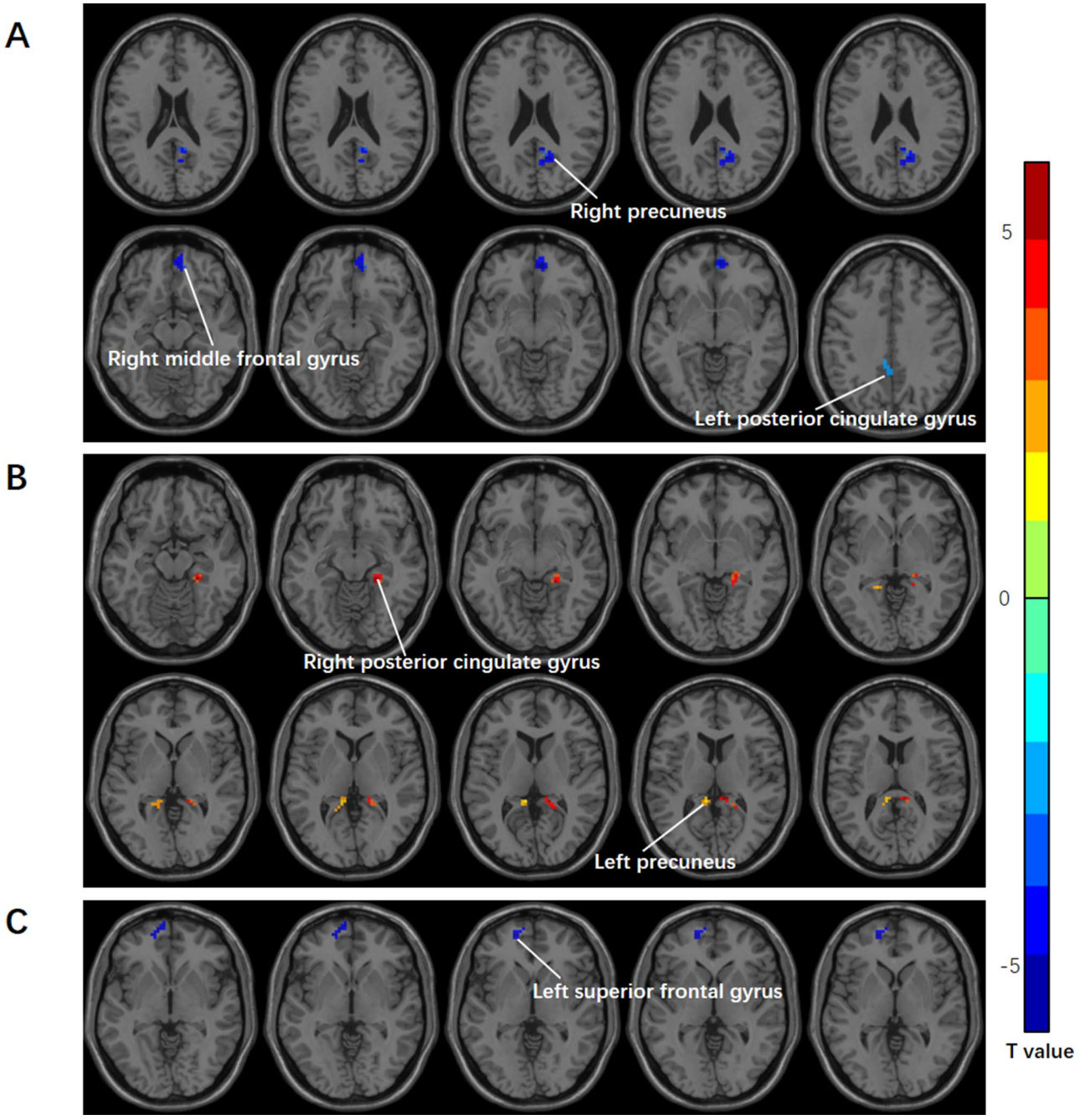

Fig. 2 The intergroup differences in local brain function. **A**, Compared with the healthy control group, the BDNSI group had decreased low-frequency fluctuations (ALFF) values in the right precuneus and decreased fractional amplitude of low-frequency fluctuation (fALFF) values in the right middle frontal gyrus and left posterior cingulate gyrus. **B**, Compared with the HC group, the BDSI group had increased ALFF values in the right posterior cingulate gyrus and left precuneus. **C**, Compared with the BDSI group, the BDNSI group had decreased fALFF values in the left superior frontal gyrus

second hypothesis, we found a significant negative correlation between Hcy levels and both verbal learning and visual learning scores. Moreover, Hcy levels were significantly and positively correlated with fALFF signals in the left posterior cingulate gyrus. This finding is partially consistent with that of a previous study in which a negative correlation was observed among Hcy levels and attention/vigilance, verbal learning, and visual learning scores [49]. Ample evidence indicates that Hcy plays a crucial role in cognitive deficits [16, 50]. For instance, previous studies have reported that homocysteinemia is associated with decreased cognitive performance in both immediate or delayed memory tests and overall cognitive function in older adults [50]. Additional studies have

Table 2 Relationships between peripheral Hcy with cognitive deficits in BDSI and BDNSI

Measure	BDNSI		BDSI	
	r-value	*P*-value	*r*-value	*P*-value
SoP	-0.146	0.528	-0.267	0.300
AV	-0.041	0.861	-0.506	**0.038**
WM	0.049	0.834	-0.053	0.840
VrbL	-0.192	0.404	-0.566	**0.018**
VisL	-0.099	0.668	-0.556	**0.020**
Right precuneus (ALFF)	0.311	0.171	0.431	0.084
Right middle frontal gyrus (ALFF)	0.100	0.665	0.415	0.097
Right posterior cingulate gyrus (ALFF)	-0.164	0.477	0.477	0.721
Left precuneus (fALFF)	0.086	0.711	-0.303	0.237
Left superior frontal gyrus (fALFF)	0.090	0.697	0.460	0.063
Left posterior cingulate gyrus (fALFF)	-0.148	0.523	0.644	**0.005**

Abbreviations: SoP, speed of processing; AV, attention/vigilance; WM, working memory; VrbL, verbal learning; VisL, visual learning; fALFF, fractional amplitude of low-frequency fluctuations; ALFF, amplitude of low-frequency fluctuations

indicated that a significantly worse performance on neurocognitive tests is associated with "elevated" Hcy levels, supporting the hypothesis that increased Hcy levels may contribute to the pathophysiology of neurocognitive deficits in BD [11].

In the BDNSI group, no relationship was found between Hcy levels and the posterior cingulate gyrus or cognitive deficits. One explanation for this is that the etiology of cognitive deficits in BDNSI may not be well understood. In previous studies, factors such as immunity, current symptoms, psychotropic medications, genetics, and previous disease course—especially the number of manic episodes, hospitalization length, and disease duration—were associated with poorer neuropsychological outcomes in BD [51–55]. Another possibility is that during the phase of increased Hcy in non-suicidal patients, it affects areas that may be more prominent, such as the hippocampus, prefrontal cortex, and right cingulum of the cingulate cortex, but not the posterior cingulate gyrus [36, 56, 57].

Mediation of cognitive function by the left posterior cingulate gyrus

We also observed that the relationship between Hcy levels and the Hcy- visual learning and verbal learning scores was mediated by the left posterior cingulate gyrus. This suggests that oxidative stress, endothelial dysfunction, inflammation, smooth muscle cell proliferation, and endoplasmic reticulum stress induced by Hcy may significantly influence cognitive function [58, 59]. Previous research has shown that oxidative stress and inflammation can induce various forms of cellular damage, raising the question of whether increased oxidative stress leads to neuropathological abnormalities [60]. Moreover, neuroinflammation may impact clinical manifestations and cognitive function by altering brain structures, such as the anterior cingulate cortex in patients with BD [61]. Individuals with BD have been shown to exhibit higher levels of lipid peroxidation and oxidative stress in their cingulate cortex [60]. The primary posterior cortical area of the default network, the most active node in the default network, and a key component of the memory and learning networks include the posterior cingulate gyrus [62]. We speculate that varying levels of Hcy between the BDSI and BDNSI groups reflect different levels of inflammation or oxidative stress conditions, leading to distinct effects on brain activity and altered fALFF values in the posterior cingulate.

Interestingly, we observed no difference in the fALFF of the posterior cingulate between the two groups of patients. This indicates that the neural activity intensity in the posterior cingulate of the two groups does not differ significantly, and correspondingly, their cognitive functions also show no significant differences. This may be due to a compensatory mechanism in BD patients,

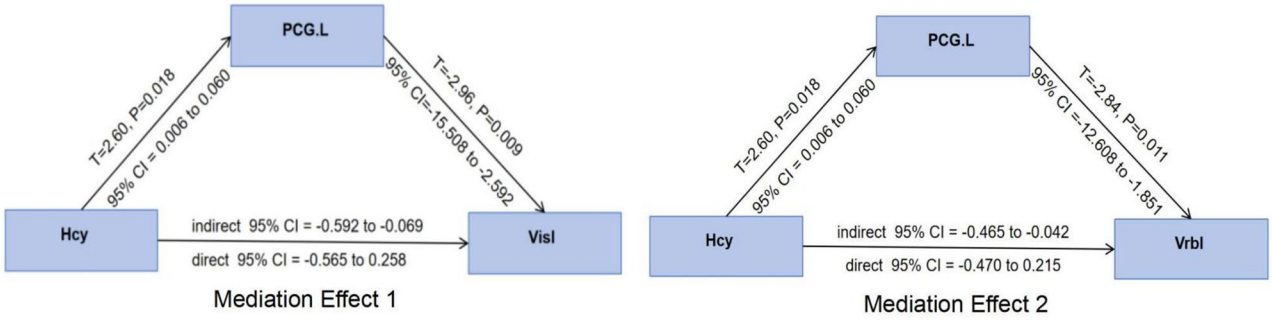

Fig. 3 Mediation models of the Hcy-brain-cognition relationship in bipolar disorder with suicidal ideation. Mediation Effect 1 shows that after accounting for significant negative indirect mediating effects (indirect 95% CI= −0.592 to −0.069) between Hcy and VisL, the remaining direct effects became non-significant (direct 95% CI= −0.565 to 0.258). Mediation Effect 2 illustrates that after accounting for significant negative indirect mediating effects (indirect 95% CI = −0.465 to −0.042) between Hcy and VrbL, the remaining direct effects became non-significant (direct 95% CI= −0.470 to 0.215). Abbreviations: CI, confidence interval; Hcy, homocysteine; VrbL, verbal learning; VisL, visual learning; L, left posterior cingulate gyrus

which allows their cognitive functions to remain normal, such as the functional and structural compensations mentioned in previous studies [63, 64]. Therefore, the two groups of BD patients in this study may also exhibit neural activity compensation in the posterior cingulate, ultimately leading to no significant differences in neural activity in this brain region.

Future research and clinical practice

Our preliminary research indicates that the neural activity in the left posterior cingulate mediates the relationship between Hcy levels and cognitive impairment. Future research should further explore the pathogenic effects of different Hcy levels and their link to inflammation and oxidative stress in the posterior cingulate of BD patients. Also, increasing the sample size would help confirm the reliability of these results. Animal model studies are also needed to better observe the relationship between neural function and Hcy levels. Our findings also have clinical implications. Currently, lithium is the main treatment for SI in BD patients [65], and TMS is an effective adjunct therapy [66]. The posterior cingulate, which we found to be related to SI in BD patients, could be a potential TMS target. A study on targeting the anterior cingulate with transcranial direct current stimulation showed improved task performance in BD patients [67]. Future clinical research should verify the posterior cingulate as a TMS target.

Limitations

Our study has some limitations. First, Hcy levels were not included in HC, limiting the comprehensiveness of our findings and comparative analysis. We will highlight that future studies should consider including Hcy levels in HC provide a more comprehensively understand the correlation between Hcy levels and MCCB scores as well as fMRI activity. Additionally, we did not collect comprehensive information on medication use in individuals with BD, leaving the potential confounding effects of psychotropic medications unaddressed in our findings. Second, the sample size was relatively small, and our findings require validation in larger cohorts. Lastly, the study utilized a case-control design; therefore, future investigations should adopt longitudinal methodologies to confirm the causal link between abnormal Hcy metabolism in the brain and cognitive deficits in individuals with BDSI.

Conclusions

Cognitive deficits in individuals with BDSI appear to be associated with elevated Hcy levels and increased fALFF signals in the posterior cingulate gyrus. The posterior cingulate gyrus mediated the significant correlation between Hcy levels and verbal learning and visual learning scores found only in individuals with BDSI, suggesting that the posterior cingulate gyrus may play a critical role in the pathophysiology of neurocognitive deficits associated with varying Hcy levels.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06925-x.

Supplementary Material 1

Author contributions

Wuchun Feng and XingBing Huang conceived and designed the study. Yuanyuan Huang, Sumiao Zhou, and Shixuan Feng performed the testing and data collection and drafted the manuscript. Hehua Li, Yuanyuan Huang, Ziyun Zhang, Chenyu Liu, Junhao Li, Kai Wu and Wei Han performed data analysis and interpretation. All the authors contributed to the manuscript and approved the submitted version.

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Data availability

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

Declarations

Ethics approval and consent to participate

All procedures in this study were conducted in accordance with the Declaration of Helsinki, and the current study was approved by the ethics committee of Affiliated Brain Hospital of Guangzhou Medical University. All participants signed informed consents during recruiting.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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