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Episode-Related Inflammation Predicts Long-Term Executive Dysfunction in Bipolar Disorder: A Longitudinal Study

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Abstract

Background

Bipolar disorder (BD) is a severe and chronic mental illness characterized by significant neurocognitive deficits, with immune dysregulation proposed as a potential mechanism. This study investigated the self-alterations and potential relationships between inflammatory markers and neurocognitive function across mood states in BD, as well as to uncover trait or state markers related to BD.

Methods

We included 84 BD patients (45 followed into euthymia) and 40 healthy controls (HCs) matched for sex, age, and BMI. All participants underwent a comprehensive neuropsychological assessment battery, and had plasma levels of ten inflammatory markers measured. Cross-sectional and longitudinal relationships between inflammation and neurocognition were examined using general linear regression and cross-lagged panel models, with false discovery rate (FDR) correction.

Results

BD patients exhibited persistent executive dysfunction (FDR-$P < 0.05$), with episodic impairments in memory, attention, and visuospatial function (all FDR-$P < 0.01$). During episodes, patients exhibited elevated pro-inflammatory markers (IL-1β, IL-2, sIL-6R, IL-12, TNF-α, IFN-γ, VEGF-A and MCP-1) and reduced anti-inflammatory markers (IL-4 and IL-10) (all FDR-$P < 0.01$). Longitudinal analyses revealed a recovery of anti-inflammatory marker levels, whereas pro-inflammatory marker levels remained persistently elevated (all FDR-$P < 0.01$). Furthermore, baseline sIL-6R ($\beta = -0.271$, $P = 0.002$) and IL-12 ($\beta = -0.431$, $P<.001$) significantly predicted poorer long-term executive function.

Conclusions

Pro-inflammatory markers demonstrate trait-like stability, whereas anti-inflammatory markers and neurocognition are more state-dependent. Notably, elevated sIL-6R and IL-12 contribute to sustained executive dysfunction, highlighting them as potential intervention targets.

1. Background

Bipolar disorder (BD) ranks as the fifth leading cause of years of life lived with disability (YLDs) among all diseases in individuals aged 15–44 years[1]. Neurocognitive dysfunction, a core symptom of BD, affects specific or global cognitive domains including attention, memory, language and executive function[2] in approximately two-third (66.7%) of BD patients[3]. In addition, neurocognitive dysfunction in

BD is evident from the first episode and may persist during remission[4]. Despite directly contributing to occupational and interpersonal disabilities, early prediction of neurocognitive function is challenging, which might somehow prevent successful targeted treatment.

Recently, emerging evidence has indicated that inflammation may play a role in the occurrence and development of BD[5–6]. Inflammatory markers have been found to impact the function, activity, and plasticity of brain neurons[7], and may be associated with neurocognitive dysfunction in BD[8]. Previous studies have revealed that specific neurocognitive capacities are negatively correlated with levels of IL-6, CRP, TNF-α and sTNFR3[9–12], while positively correlated with sTNFR2, VEGF-C levels and the ratio of IL-6 / IL-10 in BD[12–14]. However, a meta-analysis of 75 studies found only weak associations between blood-based immune markers and neurocognitive performance across global or partial domains in psychotic and mood disorders, either combined or stratified by diagnostic subgroup[15]. These cross-sectional assessments of inflammatory markers may be insufficient to capture long-term immunological effects on cognitive performance because peripheral immunomarker levels can fluctuate significantly over time, whereas cognitive deficits in mood disorders tend to be more stable or progress slowly[15]. Given the multifaceted and evolving nature of both processes, longitudinal characterization of inflammatory markers and neurocognitive prognosis over longer time periods may be necessary to assess the intricate interplay between inflammatory mechanisms and cognitive performance. Moreover, few studies to date have addressed the strength and directionality of relationships between circulating inflammation and neurocognitive function, which are essential to understand causality.

In the present study, we performed both cross-sectional and longitudinal analyses of peripheral inflammation and neurocognitive function in patients with BD during mood episodes and euthymia to clarify the relationship between immune alterations and cognitive functioning and to identify potential trait- and state-related markers.

2. Methods

2.1 Participants

A total of 84 BD patients (36 patients in hypomanic/manic, 48 patients in depressive) and 40 age, gender, and BMI matched healthy controls (HCs) were enrolled in the study. All BD patients were recruited from the outpatient or inpatient department of the Mental Health Center of West China Hospital of Sichuan University. Diagnostic eligibility was confirmed by at least two trained physicians using the patient version of the Structured Clinical Interview for Mental Disorders (SCID), fifth edition. The inclusion criteria for BD patients were: (1) aged 16–55 years; (2) a minimum of six years of formal education; (3) diagnosed with BD according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), with confirmation of a current manic, hypomanic or depressive episode; (4) had abstained from medication for at least a month; and (5) capable of understanding and completing self-assessment questionnaires. The exclusion criteria included: (1) meeting the diagnostic criteria for

any other psychiatric disorders according to the DSM-5; (2) significant comorbid physical conditions such as immune, neurological or cardiovascular disease; (3) a history of electroconvulsive therapy or loss of consciousness; (4) any use of psychiatric medications, antibiotics, immunosuppressive drugs or psychotherapy for at least one month prior to assessment.

HCs were recruited from the local communities through advertising. Their inclusion criteria were: (1) 16–55 years old; (2) not meeting the diagnostic criteria of SCID (Non-patient Version); (3) absence of infectious or autoimmune diseases, traumatic brain injury, or other severe physical issues; (4) any use of antibiotics or immunosuppressive drugs for at least one month prior to assessment; and (5) no first-degree family history of psychiatric illness.

Participants were all right-handed Han Chinese. The study was approved by The Ethics Committee of Sichuan University West China Hospital (Reference No. 2021(943)), which is in line with the Declaration of Helsinki. All participants signed informed consent.

2.2 Baseline Assessments

Upon enrollment, demographic data including age, gender, height, weight, and years of education were recorded for all participants. For patients, clinical characteristics such as age of onset, number of previous mood episodes, subtype of BD, and number of psychiatric hospitalizations were additionally collected using the SCID. Symptom severity was assessed using the 24-item Hamilton Depression Rating Scale (HAMD-24), the Hamilton Rating Scale for Anxiety (HAMA), the Young Mania Rating Scale (YMRS) and the Positive and Negative Syndrome Scale (PANSS).

Venous blood was collected on the first day after enrollment. Samples were gently inverted to prevent coagulation and centrifuged at 3180 r/min for 5 minutes. Plasma was aliquoted and stored at -80℃ until assayed. Levels of plasma inflammatory markers, including eight pro-inflammatory markers (IL-1β, IL-2, sIL-6R, IL-12, TNF-α, IFN-γ, VEGF-A, MCP-1) and two anti-inflammatory markers (IL-4, IL-10), were detected by Enzyme-linked immunosorbent assay (ELISA) using commercial kits (Ruixinbio, Quanzhou, China) in strict accordance with the manufacturer's protocols.

Within three days following enrollment, participants completed a comprehensive assessment of neurocognitive function using the MATRICS Consensus Cognitive Battery (MCCB) and the figure delayed memory test within three days after enrollment. The Chinese version of the MCCB was translated and revised by the team of Professor Yu Xin from the Sixth College of Peking University, and a Chinese population norm with good psychometric characteristics was established[16]. The Symbol Coding (SC) from the Brief Assessment of Cognition in Schizophrenia (BACS), Trail Making Test-A (TMT-A) and the Digit Span Test (DST) of the Wechsler Memory Scale-III (WMS-III) were used to evaluate executive function. The Verbal Fluency Test (VFT) was used to assess language function, and the Continuous Performance Test-Identical Pairs (CPT-IP) was used for attention. The Hopkins Verbal Learning Test-Revised (HVLT-R) for language learning and memory function, the Brief Visuospatial Memory Test-Revised (BVMT-R) for visuospatial function, and the mazes in the Neuropsychological Assessment

Battery (NAB) were used to assess reasoning and problem-solving skills. Except for the scores of TMT-A, higher scores indicate better neurocognitive performance. Based on previous classification[17], the tests were grouped into four neurocognitive domains:

1. Executive function: processing speed (TMT-A, BACS-SC and VFT), working memory (DST), and reasoning/problem-solving (the mazes);
2. Memory: verbal learning and memory (HVLT-R) and figure delayed memory;
3. Attention: CPT-IP;

(4) Visuospatial function: BVMT-R.

2.3 Follow-up Assessments

Follow-up assessments were conducted for BD patients during euthymia, operationally defined as a HAMD total score of ≤ 7, a YMRS score of ≤ 5, and sustained clinical stability for at least one month. At follow-up visits, participants replicated the baseline procedure including peripheral blood sampling and neurocognitive function testing.

2.5 Statistical Analysis

Statistical analyses were conducted using version 29.0 of the Statistical Package for Social Science (SPSS). Descriptive statistics were represented as means and SDs, medians and interquartile ranges, or frequencies. Data normality was assessed using the Shapiro-Wilk test. Demographic differences between BD patients and HCs were assessed using chi-square tests (for categorical variables), independent Student's t-tests (for normally distributed continuous variables), and Mann-Whitney U tests (for non-normally distributed continuous variables).

Longitudinal alterations in levels of inflammatory marker and neurocognitive function were assessed in BD patients following treatment were assessed using the paired-sample *t*-tests (for normally distributed differences) or Wilcoxon signed-rank tests (for non-normally distributed differences). Generalized linear regression models were constructed to examine cross-sectional associations between inflammatory markers and neurocognitive function at onset and remission, with adjustments for demographic covariates (age, sex, BMI, and education duration) and clinical characteristics (YMRS, HAMD, PANSS, and HAMA total scores). To investigate the longitudinal and potentially causal relationships between inflammation and neurocognition, we used multivariate linear regression followed by a bivariate cross-lagged panel analysis using Mplus 8.3 across two time points. The model estimated autoregressive paths (stability of each construct over time) and cross-lagged paths (predictive effects between constructs across time), while accounting for concurrent within-time correlations and residual autocorrelations. All continuous variables were grand-mean centered, and models were adjusted for relevant demographic and clinical covariates, with full-information maximum likelihood used to handle missing data. Model fit was considered acceptable if the following criteria were met: Comparative Fit Index (CFI) and Tucker Lewis index (TLI) > 0.90, root-mean-square error of approximation (RMSEA) < 0.08, and standardized root-mean-square residual (SRMR) < 0.08[18].

The study flowchart, including the final sample sizes for each analysis, is presented in Fig. 1. A two-tailed *P* value < 0.05 was defined as the threshold for statistical significance, and the false discovery rate (FDR) was applied to correct for multiple comparisons.

3. Results

3.1 Demographic and clinical characteristics

The demographic and clinical details of the 84 BD patients and 40 HCs are presented in Table 1. The two groups were well-matched in terms of age, sex, and BMI, except for the significantly higher years of education in HCs. Clinically, BD patients exhibited psychotic symptoms (as assessed by the PANSS) and had a median medication-free period of approximately 7.5 months.

Table 1
Demographic and clinical characteristics of BD patients and HCs.

Age (years)	**BD (N = 84)**	**HC (N = 40)**	***t* / *Z* / χ^2**	***P***	**Group Comparisons**
	21.00 (11.00)	**21.50 (6.00)**	**-1.766**	**0.077**	**BD ~ HC**
Sex (m/f)	28/46	15/25	0.208	0.649	BD ~ HC
BMI (kg/m^2)	21.58 (4.98)	20.81 (4.98)	-0.458	0.647	BD ~ HC
Education (years)	14.00 (5.00)	15.00 (1.00)	-3.319	< 0.001	BD < HC
Age of onset (years)	17.00 (7.00)	-	-	-	-
Subtype (BD-I/BD-II)	35/49	-	-	-	-
Duration of illness (months)	36.00 (49.00)	-	-	-	-
Previous mood episodes (times)	2.00 (1.00)	-	-	-	-
Psychiatric hospitalization (times)	1.00 (1.00)	-	-	-	-
Duration of current mood episode (weeks)	2.00 (5.00)	-	-	-	-
Not on medication (months)	7.50 (35.00)	-	-	-	-
YMRS scores	6.00 (14.00)	-	-	-	-
HAMD-24 scores					
Anxiety/somatization	2.00 (3.00)	-	-	-	-
Weight	0.00 (0.00)	-	-	-	-
Cognitive Disturbance	3.00 (4.00)	-	-	-	-
Diurnal Variation	0.00 (1.00)	-	-	-	-

Note: Unless otherwise indicated, data are means (SD) or median (inter-quartile); BD, bipolar disorder; HCs, healthy controls; BMI, Body Mass Index; YMRS, the Young Manic Rating Scale; HAMD-24, the 24 Items- Hamilton Depression scale; HAMA, the Hamilton Anxiety Scale; PANSS, Positive and Negative Syndrome.

Age (years)	BD (N = 84)	HC (N = 40)	t / Z / χ^2	P	Group Comparisons
	21.00 (11.00)	**21.50 (6.00)**	**-1.766**	**0.077**	**BD ~ HC**
Block	4.50 (4.00)	-	-	-	-
Sleep	1.00 (3.00)	-	-	-	-
Despair	3.00 (5.00)	-	-	-	-
Total	15.86 (9.48)	-	-	-	-
HAMA scores					
Somatic	2.00 (7.00)	-	-	-	-
Psychotic	8.48 (4.80)	-	-	-	-
Total	10.00 (11.00)	-	-	-	-
PANSS scores					
Positive	10.00 (7.00)	-	-	-	-
Negative	7.00 (3.00)	-	-	-	-
Psychotic	26.00 (12.00)	-	-	-	-
Total	44.42 (14.55)	-	-	-	-

Note: Unless otherwise indicated, data are means (SD) or median (inter-quartile); BD, bipolar disorder; HCs, healthy controls; BMI, Body Mass Index; YMRS, the Young Manic Rating Scale; HAMD-24, the 24 Items- Hamilton Depression scale; HAMA, the Hamilton Anxiety Scale; PANSS, Positive and Negative Syndrome.

3.2 Neurocognitive function comparisons

3.2.1 Neurocognitive function comparisons at baseline

Eight BD patients failed to complete neurocognitive tests due to the severity of their symptoms. Consequently, a total of 76 BD patients and 40 HCs were ultimately included in the baseline neurocognitive comparisons. BD patients underperformed HCs in terms of executive function (BACS-SC:

FDR-*P* < 0.01; VFT: FDR-*P* = 0.016; DST: FDR-*P* = 0.006; NAB Mazes: FDR-*P* = 0.006), memory, attention, and visuospatial function (all FDR-*P* < 0.01). However, no significant difference in TMT-A performance was observed between the two groups (Table 2).

Table 2
Comparisons of neurocognitive function among BD and HC groups at baseline.

		BD (N = 76)	HC (N = 40)	*t* / *Z*	FDR-*P*	Group Comparisons
Executive Function						
	TMT-A	34.67 (17.51)	32.43 (9.54)	-1.534	0.125	BD ~ HC
	BACS-SC	57.75 (11.66)	69.75 (9.47)	5.595	< 0.01	BD < HC
	VFT	22.15 (5.97)	25.03 (5.24)	2.568	0.016	BD < HC
	DST	21.92 (4.00)	24.45 (4.76)	3.024	0.006	BD < HC
	NAB Mazes	19.00 (9.00)	22.00 (7.00)	-3.023	0.006	BD < HC
Memory						
	Figure Delayed Memory	17.40 (7.72)	23.68 (7.67)	4.169	< 0.01	BD < HC
	HVLT-R	26.00 (8.00)	30.00 (4.00)	-3.664	< 0.01	BD < HC
Attention	CPT-IP	2.53 (0.85)	3.08 (0.81)	-4.558	< 0.01	BD < HC
Visuospatial Function	BVMT-R	25.00 (9.00)	30.00 (7.00)	-3.896	< 0.01	BD < HC

Note: BD, bipolar disorder; HC, healthy control; FDR, false discovery rate; TMT-A, Trail Making Test-A; BACS-SC, the Brief Assessment of Cognition in Schizophrenia- Symbol Coding; DST, the Digit Span Test; NAB, Neuropsychological Assessment Battery; HVLT-R, the Hopkins Verbal Learning Test-Revised; CPT-IP, the Continuous Performance Test- Identical Pairs; VFT, Verbal Fluency Test; BVMT-R, the Brief Visuospatial Memory Test- Revised.

3.2.2 Neurocognitive function comparisons at follow-up

After excluding those who dropped out, a total of 45 BD patients were euthymic at follow-up and completed neurocognitive function tests. Euthymic BD patients performed significantly poorer than HCs on executive cognition tests, specifically on the BACS-SC (FDR-*P* < 0.01), VFT (FDR-*P* = 0.033), and DST

(FDR-*P* = 0.033) (Table 3). Longitudinal alterations of neurocognitive function in BD patients are presented in Supplementary Table 1.

Table 3
Comparisons of neurocognitive function between euthymic BD patients and HCs at follow-up.

		Euthymic BD (N = 45)	HC (N = 40)	*t* / *Z*	FDR-*P*	Group Comparisons
Executive Function						
	TMT-A	29.13 (15.57)	32.43 (9.54)	-0.674	0.501	BD ~ HC
	BACS-SC	60.78 (12.02)	69.75 (9.47)	3.789	< 0.01	BD < HC
	VFT	21.73 (6.48)	25.03 (5.24)	2.586	0.033	BD < HC
	DST	21.87 (4.32)	24.45 (4.76)	2.626	0.033	BD < HC
	NAB Mazes	21.00 (7.00)	22.00 (7.00)	-0.85	0.444	BD ~ HC
Memory						
	Figure Delayed Memory	21.91 (8.03)	23.68 (7.67)	1.035	0.305	BD ~ HC
	HVLT-R	28.00 (9.00)	30.00 (4.00)	-1.919	0.099	BD ~ HC
Attention	CPT-IP	2.89 (0.87)	3.08 (0.81)	-0.893	0.444	BD ~ HC
Visuospatial Function	BVMT-R	27.00 (9.00)	30.00 (7.00)	-2.024	0.097	BD ~ HC

Note: BD, bipolar disorder; HC, healthy control; FDR, false discovery rate; TMT-A, Trail Making Test-A; BACS-SC, the Brief Assessment of Cognition in Schizophrenia- Symbol Coding; DST, the Digit Span Test; NAB, Neuropsychological Assessment Battery; HVLT-R, the Hopkins Verbal Learning Test-Revised; CPT-IP, the Continuous Performance Test- Identical Pairs; VFT, Verbal Fluency Test; BVMT-R, the Brief Visuospatial Memory Test- Revised.

3.3 Inflammatory marker comparisons

3.3.1 Inflammatory marker comparisons at baseline

A total of 83 BD patients (with one individual declining blood sampling for personal reasons) and 40 HCs were enrolled in the baseline inflammatory marker comparisons. Levels of all pro-inflammatory markers (IL-1β, IL-2, sIL-6R, IL-12, TNF-α, IFN-γ, VEGF-A and MCP-1) were significantly higher in the BD group than

in the HC group, whereas the anti-inflammatory markers (IL-4 and IL-10) were significantly lower (all FDR-*P* < 0.01) (Table 4A).

3.3.2 Inflammatory marker comparisons at follow-up

Despite achieving euthymia at follow-up, 45 BD patients (with one declining blood sampling) exhibited a persistent, broad pro-inflammatory state compared to HCs. This was characterized by significantly elevated levels of multiple pro-inflammatory markers (IL-1β, IL-2, sIL-6R, IL-12, TNF-α, IFN-γ, VEGF-A, and MCP-1) and a relative deficit in the anti-inflammatory cytokine IL-10 (all FDR-*P* < 0.01; Table 4B). Notably, this inflammatory profile was observed despite longitudinal increases in two anti-inflammatory markers (Supplementary Table 2).

Table 4
Comparisons of Inflammatory Marker Levels Between BD Patients and HCs. (A) Comparisons at Baseline (Symptomatic Phase for BD).

	BD(N = 83)	**HC (N = 40)**	***t / Z***	**FDR-*P***	**Group Comparisons**
Pro-inflammatory markers (pg/ml)					
IL-1β	66.03 (18.19)	45.16 (18.16)	-7.98	< 0.01	BD > HC
IL-2	700.96 (160.46)	451.73 (80.89)	-8.704	< 0.01	BD > HC
sIL-6R	127.70 (28.84)	73.89 (39.83)	-8.26	< 0.01	BD > HC
IL-12	39.74 (20.30)	12.71 (6.60)	-8.881	< 0.01	BD > HC
TNF-α	63.21 (16.91)	32.94 (8.92)	-8.854	< 0.01	BD > HC
IFN-γ	711.37 (188.39)	421.61 (163.76)	-8.29	< 0.01	BD > HC
VEGF-A	348.70 (87.37)	273.88 (82.43)	-7.478	< 0.01	BD > HC
MCP-1	276.77 (66.06)	198.01 (35.97)	-8.025	< 0.01	BD > HC
Anti-inflammatory markers (pg/ml)					
IL-4	24.56 (9.97)	34.40 (5.60)	-6.479	< 0.01	BD < HC
IL-10	537.73 (101.25)	794.71 (93.55)	13.508	< 0.01	BD < HC

(B) Comparisons at Follow-up (Euthymic Phase for BD).

	Euthymic BD (N = 44)	HC (N = 40)	*t* / *Z*	FDR-*P*	Group Comparisons
Pro-inflammatory markers (pg/ml)					
IL-1β	59.06 (40.25)	45.16 (18.16)	-3.882	< 0.01	BD > HC
IL-2	673.21 (294.67)	451.73 (80.89)	-6.024	< 0.01	BD > HC
sIL-6R	123.97 (90.52)	73.89 (39.83)	-5.459	< 0.01	BD > HC
IL-12	42.47 (16.57)	12.71 (6.60)	-7.838	< 0.01	BD > HC
TNF-α	58.32 (41.63)	32.94 (8.92)	-6.607	< 0.01	BD > HC
IFN-γ	655.21 (397.35)	421.61 (163.76)	-5.35	< 0.01	BD > HC
VEGF-A	327.48 (180.22)	273.88 (82.43)	-3.928	< 0.01	BD > HC
MCP-1	248.16 (87.71)	198.01 (35.97)	-3.946	< 0.01	BD > HC
Anti-inflammatory markers (pg/ml)					
IL-4	33.69 (10.82)	34.40 (5.60)	-0.374	0.709	BD ~ HC
IL-10	705.32 (162.76)	794.71 (93.55)	-4.156	< 0.01	BD < HC
Note: BD, bipolar disorder; HC, healthy control; FDR, false discovery rate.					

3.4 Associations between neurocognitive function and inflammatory markers

3.4.1 Cross-sectional associations between neurocognitive function and inflammatory markers

After controlling for key demographic (age, sex, BMI, and years of education) and clinical covariates (YMRS, HAMD, PANSS, and HAMA total scores), general linear regression models revealed several cross-sectional associations between neurocognitive function and inflammatory markers in BD. Specifically, poorer scores on the BACS-SC (B = -0.096, SE = 0.034, β = -0.307, t = -2.833, *P* = 0.006) and VFT (B = -0.043, SE = 0.018, β = -0.273, t = -2.342, *P* = 0.022) were associated with higher levels of MCP-1, and poorer HVLT-R performance was linked to higher IL-12 (B = -0.121, SE = 0.051, β = -0.267, t = -2.384, *P* = 0.020) but lower levels of IL-2 (B = 0.013, SE = 0.006, β = 0.242, t = 2.191, *P* = 0.032). However, it should be explicitly noted that none of the observed associations withstood the Benjamini-Hochberg FDR correction procedure (all FDR-*P* > 0.05). Therefore, these findings should be interpreted strictly as exploratory outcomes for variable selection rather than as statistically robust discoveries.

To address concerns regarding model overfitting and inferential stability given the available sample size, we conducted stratified regression analyses adjusting solely for demographic covariates. In this model, associations were observed between IL-2 and HVLT-R performance (B = 0.017, SE = 0.008, β = 0.317, t =

2.199, *P* = 0.032), and between MCP-1 and VFT (B = -0.046, SE = 0.020, β = -0.290, t = -2.324, *P* = 0.024) prior to multiple comparison adjustment. Notably, associations of MCP-1 with BACS-SC and of IL-12 with HVLT-R identified in the full model were absent in the demographics-only model. Conversely, the demographics-only model revealed additional links between TNF-α, IL-4, IFN-γ and VFT that were not evident in the full model. None of these associations survived FDR correction. Detailed results are provided in the Supplementary.

3.4.2 Longitudinal associations between neurocognitive function and inflammatory markers

To identify candidate variables for inclusion in subsequent cross-lagged analyses, we first conducted exploratory linear regression analyses. Given the screening purpose of this stage, multiple comparison correction was not applied, and associations with *P* < 0.05 (uncorrected) were selected for further modeling. The preliminary screening results are presented in Table 5.

Table 5
Predictive Role of Baseline Inflammation for Longitudinal Neurocognitive Outcomes in BD.

Outcome (Follow-up)	**Predictor (Baseline)**	**B**	**SE**	**β**	***t***	***P***
VFT	IL-12	-0.22	0.077	-0.43	-2.857	0.007
DST	sIL-6R	-0.069	0.033	-0.327	-2.076	0.045
TMT-A	sIL-6R	-0.3	0.113	-0.33	-2.652	0.012
TMT-A	VEGF-A	0.108	0.047	0.288	2.308	0.027

Note: B, unstandardized coefficient; SE, standard error; β, standardized coefficient; VFT, Verbal Fluency Test; DST, the Digit Span Test; TMT-A, Trail Making Test-A.

Then, cross-lagged path analyses were carried out to verify the relationship and determine the directionality. In BD patients, baseline IL-12 levels were negatively correlated with VFT performance at follow-up unidirectionally (β = -0.431, SE = 0.104, 95% CI [-0.635, -0.227], *P* < 0.001), not vice versa (β = -0.042, SE = 0.161, 95% CI [-0.358, 0.274], *P* = 0.794) (Fig. 2A). This model showed an excellent fit: $\chi^2(16) = 16.25$, *P* = 0.436; CFI = 0.979, TLI = 0.951, RMSEA = 0.020, SRMR = 0.066). And sIL-6R level during episodes could negatively predict euthymic DST performance (β = -0.271, SE = 0.086, 95% CI [-0.440, -0.102], *P* = 0.002), not vice versa (β = 0.125, SE = 0.166, 95% CI [-0.200, 0.450], *P* = 0.456) (Fig. 2B). The model fit was also excellent: $\chi^2(16) = 12.94$, *P* = 0.677; CFI = 1.000, TLI = 1.300 (a value exceeding 1.0, which occurs when the model's fit approaches empirical saturation), RMSEA < 0.001, SRMR = 0.056. Both associations remained statistically significant after applying FDR correction (all FDR-*P* < 0.05).

Analyses controlling only for demographic covariates (age, sex, BMI, and years of education) confirmed baseline IL-12 as a robust longitudinal predictor of worse VFT performance (β = -0.409, SE = 0.125, 95% CI [-0.653, -0.165], *P* < 0.001). Divergent findings also emerged, such as a significant longitudinal

association between IL-1β and Figure Delayed Memory that was not evident in the full model. Complete results are available in the Supplementary.

4. Discussion

In this study, we conducted cross-sectional and longitudinal analyses to explore the intricate relationship between inflammatory markers and neurocognitive performance across mood states in individuals with bipolar disorder (BD). Our findings revealed that BD patients exhibited widespread neurocognitive impairments during mood episodes, concomitant with a pro-inflammatory state characterized by elevated levels of IL-1β, IL-2, sIL-6R, IL-12, TNF-α, IFN-γ, VEGF-A, and MCP-1, as well as reduced anti-inflammatory cytokines (IL-4 and IL-10). Compared with episodes, euthymia was associated with partial recovery in neurocognitive deficits and anti-inflammatory markers, while pro-inflammatory markers remained persistently elevated. Importantly, associations between inflammatory markers and neurocognitive performance were evident primarily in longitudinal analyses, with baseline elevations in sIL-6R and IL-12 predicting subsequent executive dysfunction. Together, these findings suggest that dysregulated inflammatory signaling may contribute to long-term cognitive decline in BD and highlight inflammatory pathways as potential targets for improving cognitive outcomes.

4.1 Inflammatory abnormalities in BD

The present study revealed consistently elevated pro-inflammatory markers (including IL-1β, IL-2, sIL-6R, IL-12, TNF-α, IFN-γ, VEGF-A and MCP-1) in BD patients across various mood states, suggesting the presence of persistent immune dysregulation in the illness. In line with our findings, previous case-control studies have reported increased pro-inflammatory activity not only during acute episodes[19–22] but also during euthymia[23–24]. A meta-analysis encompassing 49 studies further confirmed that IL-6 levels remained elevated regardless of disease state[25]. Meanwhile, our longitudinal analyses indicated no significant decline in pro-inflammatory markers as clinical symptoms improve. Similarly, a previous study reported no significant sTNF-R1 alterations from baseline to one-year follow-up in affective spectrum patients (n = 55)[26], and Tsai SY et al. documented persistently elevated levels of hs-CRP, sTNF-R1 and sIL-2R in phases of BD from acute depression to full remission[27].

Conversely, anti-inflammatory markers showed a dynamic pattern that was inversely correlated with disease activity: IL-4 and IL-10 decreased during mood episodes and gradually improved with symptom improvement, yet IL-10 remained suppressed albeit IL-4 normalized. Reported levels of anti-inflammatory markers in BD are inconsistent[19, 28–29], likely due to factors such as uncategorized emotional states, uncontrolled pharmacotherapy, and comorbid metabolic diseases[22]. There is also a notable lack of longitudinal studies tracking these markers across mood phases. Therefore, our results, derived from a rigorously characterized cohort —with confirmed mood states and at least one month of medication washout—provide more credible insights. The observed increase in anti-inflammatory markers could

reflect a compensatory regulatory response and/or the neuroprotective effects of mood-stabilizing treatments[30].

Collectively, our data reinforce the hypothesis that the pathophysiology of BD may involve a sustained imbalance between pro- and anti-inflammatory mediators, potentially driven by a dysregulation in M1/M2 macrophage polarization — a process in which M1 and M2 phenotypes predominantly promote pro- and anti-inflammatory responses, respectively[31]. Our findings align with previous suggestions that multi-biomarker panels (including neurotrophins and cytokines), rather than isolated indicators, may better capture mood-state signatures in BD[32]. Building on these observations, we further propose a trait-state model of immune dysfunction in BD: pro-inflammatory markers may reflect a trait-like, persistent disturbance inherent to the disorder, whereas anti-inflammatory markers appear more state-dependent, fluctuating in relation to clinical phases.

4.2 Neurocognitive dysfunction in BD

The present study found widespread neurocognitive deficits in BD patients during episodes, encompassing impairments in executive function (including processing speed, working memory, and reasoning/problem-solving ability), memory, attention, and visuospatial abilities. Follow-up assessments of euthymic patients revealed persistent deficits, particularly in processing speed (assessed by BACS-SC and VFT) and working memory (assessed by DST), while performance in other domains was comparable to that of healthy levels. These findings are consistent with prior studies documenting significant cognitive impairments across clinical states in BD[33–35], with executive dysfunction being especially prominent[36]. However, the profile of cognitive deficits during euthymia appears heterogeneous across the literature. While some studies report comparable performances between euthymic BD patients and HCs in areas like cognitive flexibility and verbal memory[37], meta-analyses have identified moderate-to-large deficits in verbal/visual learning, memory, and working memory[38]. Other researchers have suggested that only a subgroup of euthymic patients exhibit neurocognitive impairments[39, 40]. These discrepancies likely stem from variation in sample characteristics, assessment methodologies, definitions of euthymia, and the potential existence of BD subtypes with distinct cognitive profiles.

Taken together, the available evidence indicates that executive function, specifically in processing speed and working memory, may represent a more trait-like and persistent deficit in BD, whereas other neurocognitive domains may show more state-dependent fluctuations. Future longitudinal researches employing standardized neuropsychological batteries and exploring biological correlates is crucial to clarify the trajectory, mechanisms, and individual differences in cognitive functioning across the course of BD.

4.3 Associations between neurocognitive function and inflammation

Our study revealed that elevated levels of the pro-inflammatory markers sIL-6R and IL-12 during mood episodes could predict poorer recovery in working memory or processing speed after clinical remission.

This establishes a clear temporal sequence in which peripheral inflammation precedes persistent neurocognitive impairment. Our findings extend and refine the existing literature. While a prior systematic review synthesized cross-sectional evidence linking various inflammatory markers (e.g., TNF-α, IL-6, CRP) to cognitive deficits in BD[41], it inherently cannot address the directionality or potential causality of these associations. By employing a longitudinal cross-lagged design, we directly address this gap. Our model indicates that inflammation specifically predicts subsequent cognitive decline, and not vice versa. This methodological advance provides stronger evidence for a directional pathway, moving beyond the inferences inherent to cross-sectional analyses.

We did not detect a significant association between neurocognitive function and inflammation in BD patients during episodes. The observed discrepancy between the non-significant cross-sectional association after FDR correction and robust longitudinal prediction is instructive. Cross-sectional measures may be more susceptible to transient state factors (e.g., symptom fluctuations), acute medication effects, or episodic comorbidities, which can dilute a stable neuroimmunological signal. In contrast, longitudinal modeling captures the enduring, trait-like effect of inflammatory activity on cognitive trajectories, supporting inflammation as a driver rather than a mere correlate of impairment.

The biological plausibility of our findings is supported by established neuroimmune mechanisms. Activation of the inflammatory response system (IRS) during mood episodes increases pro-inflammatory signaling, which can influence emotion, cognition, and behavior through multiple pathways, including altered neurotransmission, microglial activation, HPA-axis dysregulation, and impaired neuroplasticity[42–45]. Notably, sIL-6R and IL-12 may function as trait-like markers, given their persistence after treatment and their enduring impact from acute episodes into euthymia. Their reported associations with structural and functional brain alterations—such as cortical thinning in the right middle temporal gyrus and reduced prefrontal-limbic connectivity[46, 47] —provide a plausible neural substrate for the observed executive dysfunction[48, 49]. Our data thus integrate peripheral inflammation and measurable cognitive decline into a coherent model, suggesting that acute inflammatory surges during episodes may leave a “cognitive scar” beyond mood symptom resolution. Consequently, sIL-6R and IL-12 may serve not only as state correlates, but also as candidate prognostic biomarkers for long-term neurocognitive trajectories in BD.

4.4 Strengths and limitations

The current study has several strengths, including control for medication effects on inflammatory marker levels, rigorous mood-state classification, comprehensive neurocognitive assessment, measurement of multiple inflammatory markers, and a longitudinal design with complementary analytic approaches. In addition, key demographic characteristics such as sex and BMI were well balanced between groups.

Several limitations should also be noted. First, despite statistical adjustment, educational attainment differed slightly between BD patients and HCs (14 *vs.* 15 years), which may have introduced residual confounding. Second, although all euthymic BD patients were assessed within a 6–12 month follow-up window, the exact timing varied across participants. Future studies with fixed assessment intervals may

reduce bias related to temporal heterogeneity. Third, the longitudinal sample size was relatively moderate, limiting stratified analyses by baseline mood episode (e.g., manic *vs.* depressive). Finally, concurrent medication during euthymia may have confounded the observed inflammation-neurocognition relationship, as psychotropic treatments can affect both systems; future studies should explicitly model treatment exposure to strengthen causal inference.

4.5 Conclusion

This study demonstrates that acute-phase inflammation in bipolar disorder is prospectively associated with poorer long-term neurocognitive outcomes, particularly executive function, independent of clinical remission. These findings reframe persistent executive impairment in BD not merely as a sequela of mood symptoms but as a condition partly driven by enduring biological processes. This paradigm shift paves the way for developing novel biomarker-stratified and immunomodulatory strategies aimed at improving the often-overlooked cognitive prognosis in BD. Elucidating the mechanisms linking inflammation and cognition may also inform interventions that integrate mood stabilization with cognitive rehabilitation, ultimately improving long-term functional outcomes.

Declarations

Ethics approval and consent to participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the Ethics Committee of Sichuan University West China Hospital (Reference No. 2021(943)), which is in line with the Helsinki Declaration of 1975, as revised in 2013. Informed consent is signed by all study participants.

Consent for publication

Not Applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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agencies had no role in the design of the study, collection, analysis, and interpretation of the data, or in the writing of the manuscript, but provided the publication cost.

Authors' contributions

XFC, YGT, YX, LC and TWX collected the participant data. XFC analyzed and interpreted the data, and was a major contributor in writing the manuscript. QW and LML made the contribution to the conception and revised the manuscript. All authors read and approved the final manuscript.

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Figures

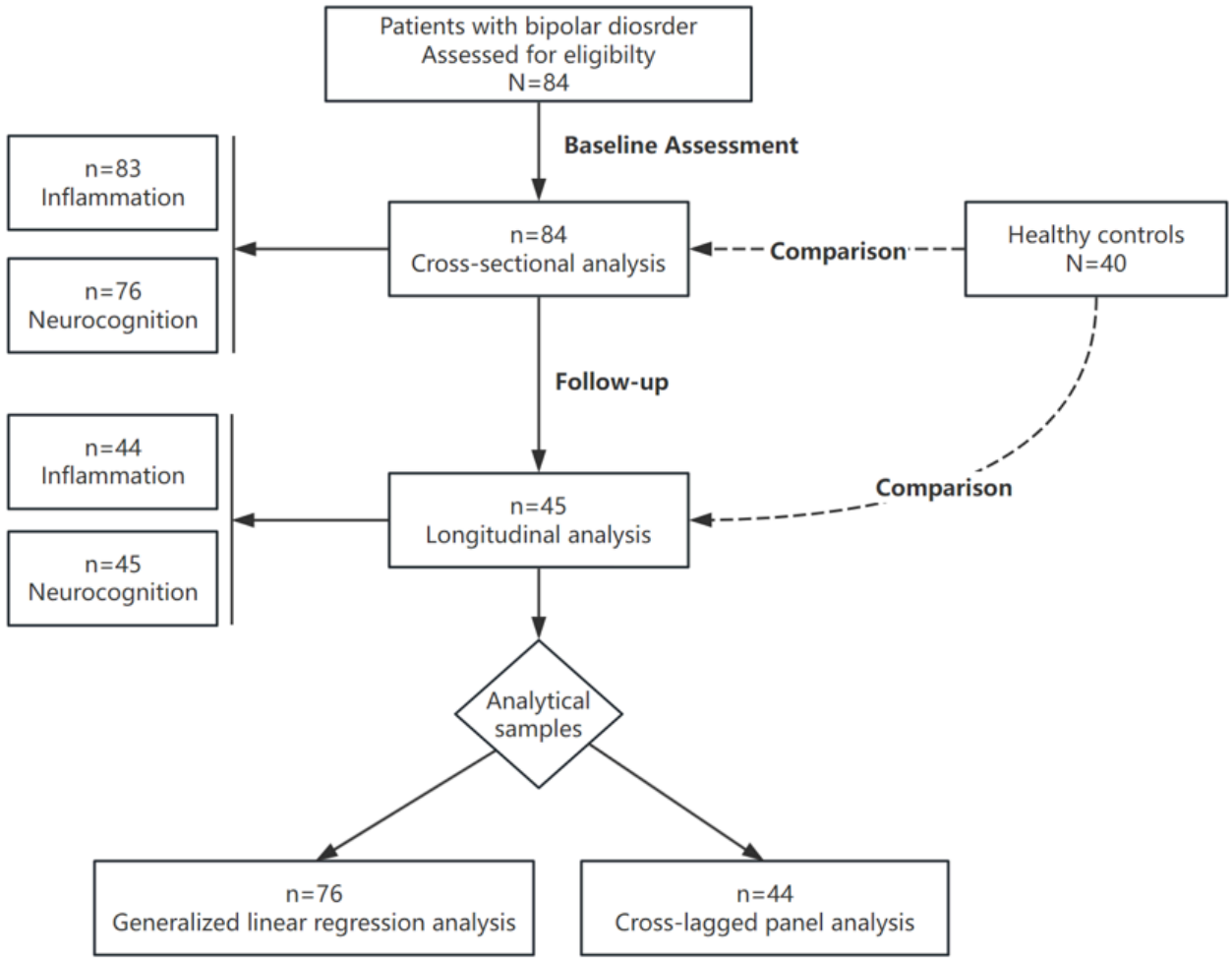


Figure 1

Participant Flow Diagram for the Cross-Sectional and Longitudinal Analyses of Inflammation and Neurocognition in Bipolar Disorder

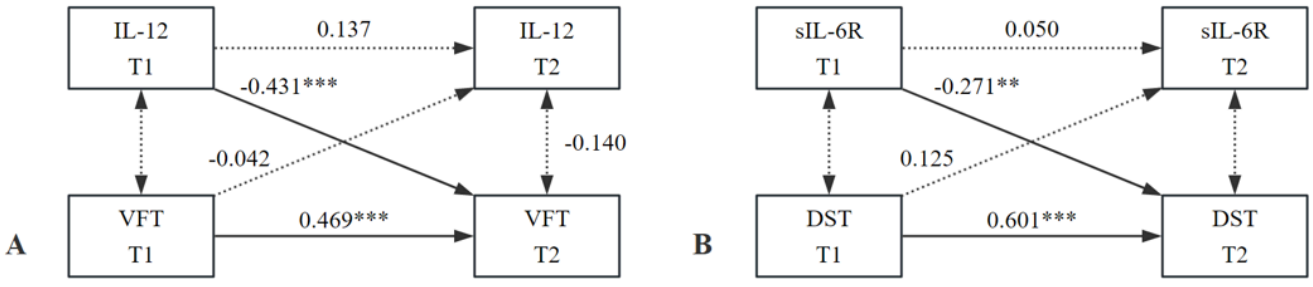


Figure 2

Standardized path diagram of cross-lagged panel model between inflammation and neurocognition.

Note: T1, at baseline; T2, at follow-up; VFT, Verbal Fluency Test; DST, the Digit Span Test. Single-headed arrows = regressions (freely estimated regression weight), double-headed arrows = correlations or covariances; Solid lines = significant paths, and dotted line = non-significant paths. To simplify the representation of the model, control variables (sex, age, BMI, educational years, total scores of YMRS, HAMD, HAMA, and PANSS) and error terms are not shown. *$P < 0.05$, **$P < 0.01$, ***$P< 0.001$.

Supplementary Files

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