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Comparison of executive dysfunction, proinflammatory cytokines, and appetite hormones between first-episode and multiple-episode bipolar disorders

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Abstract

Background. Evidence has demonstrated associations of bipolar disorder (BD) with cognitive impairment, dysregulated proinflammatory cytokines, and appetite hormones.
Aim. To compare executive dysfunction, proinflammatory cytokines, and appetite hormones between patients with first-episode and multiple-episode BDs.
Methods. This cross-sectional study included young adults aged 18 to 39 years who were diagnosed as having type 1 BD in the first or recurrent episode and a group of age-/sex-matched healthy controls. Data regarding patient characteristics, clinical symptoms, cytokines (C-reactive protein [CRP], interleukin-6, and tumor necrosis factor [TNF]-α), appetite hormones (leptin, adiponectin, ghrelin, and insulin), and executive function evaluated using the Wisconsin Card Sorting Test (WCST) were collected.
Results. A total of 112 participants (38 patients in the multiple-episode BD group, 31 patients in the first-episode BD group, and 43 in the control group) were included. Multivariate analysis revealed that patients in the multiple-episode BD group performed significantly worse in the WCST ($P < .05$) and had higher levels of ghrelin ($P = .002$), and lower levels of CRP ($P = .040$) than those in the first-episode BD group. Patients with BD had significantly higher TNF-α and ghrelin levels compared with the healthy controls. No significant associations of CRP, TNF-α, and ghrelin levels with executive function were observed.
Conclusions. Profiles in proinflammatory cytokines and appetite hormones as well as executive function significantly differed between patients with first-episode and multiple-episode BDs and controls, which may suggest their potential roles in the clinical stages and pathophysiology of type 1 BD.

Introduction

Bipolar disorder (BD) is a chronic and recurrent illness that causes severe mood disturbances, with a lifetime prevalence estimated at 1.0% worldwide.[1] BD is also one of the leading health conditions associated with disability.[2] Many researchers have compared the characteristics of patients with first-episode BD and multiple-episode BD to determine whether BD is a static or progressive disease. It was found that patients with first-episode and multiple-episode BDs show many differences; for instance, patients with first-episode BD exhibit greater functioning[3] and better treatment response[4] and have shorter hospital stays and more limited impulse control deficits.[5] In addition, the cognitive function[6] and brain structures of patients with first-episode and multiple-episode BDs differ.[7] These findings have helped us understand the disease progression of BD and have also emphasized the importance of early diagnosis and early intervention to arrest disease progression.

Previous evidence has suggested the role of inflammatory dysregulation[8,9] and altered appetite hormone profiles in BD.[10,11] Levels of C-reactive protein (CRP), interleukin (IL)-6 and tumor necrosis factor (TNF)-α were found to be significantly elevated in patients with BD than in healthy controls and were associated with the severity of the disease.[8,9] In addition, Cordas et al[10] demonstrated that patients with BD exhibit lower leptin levels than the control group. Mansur et al[11] reported that patients with BD having low adiponectin levels (<7.5 μg/mL) had fewer psychiatric hospitalizations, higher depressive symptoms, and lower functioning levels than did those with high adiponectin levels. Furthermore, BD causes not only mood fluctuations but also impaired cognitive function.[12,13] Both proinflammatory cytokines, especially CRP, and appetite hormones, such as leptin and ghrelin, may play important roles in BD-related cognitive impairment.[14-16] Chung et al[14] found a positive association between CRP

levels and executive function impairments among patients with BD. A systemic review of 555 patients with BD revealed that elevated CRP level was correlated with cognitive impairment in BD, specifically in the domains of attention and executive function.[15] Our previous study indicated a positive correlation between ghrelin levels and executive function in patients with BD.[16] However, fewer studies have investigated the role of inflammatory and appetite hormone biomarkers and executive function in the disease progression of BD.

Therefore, in this study, we aimed to compare the executive dysfunction, proinflammatory cytokines, and appetite hormones between patients with first-episode and multiple-episode BDs and evaluate the associations of proinflammatory cytokines and appetite hormones with executive dysfunction in BD.

Methods

Participants

Young adults aged between 18 and 39 years who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision or Fifth Edition (DSM-IV-TR or DSM-5) criteria for bipolar I disorder in the first episode or the recurrent episode and were in a relatively stable condition to comply with study procedures were enrolled as the study group. Age- and sex-matched healthy controls who did not have a DSM-IV-TR or DSM-5 diagnosis, who were not pregnant or breastfeeding, and who did not have a severe physical disease (ie, epilepsy, stroke, or systemic lupus erythematosus) or unstable physical illnesses were enrolled as the control group. Demographic characteristics, including the age of onset, education, and body mass index (BMI) were recorded, and clinical evaluation, such as the Young Mania Rating Scale (YMRS) and the Montgomery–Åsberg Depression Rating Scale (MADRS), were assessed. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study.

Measurement of proinflammatory cytokines and appetite hormones

Fasting serum samples were collected in serum separator tubes, clotted for 30 minutes, and stored at −80°C until use (within 4 months after collection). Proinflammatory cytokines, including IL-6, TNF-α, and CRP, were assayed using enzyme-linked immunosorbent assay (ELISA) kits (R&D systems, Minneapolis, MN) for all participants. The appetite hormones, including leptin, ghrelin, insulin, and adiponectin, were examined. Ghrelin was measured using a radioimmunoassay (RIA) kit (Peninsula Laboratories, Inc., San Carlos, CA). Insulin concentrations were analyzed using a radioimmunoassay kit (Coat-A Count Insulin; Diagnostic Product Corporation, Los Angeles, CA). Serum adiponectin level was measured using a quantitative Human Adiponectin ELISA Kit (B-Bridge International, Inc., Mountain View, CA). All assays were performed according to the vendor's instructions. The final absorbance of each sample of the mixture was measured and analyzed at 450 nm using an ELISA plate reader with Bio-Tek Power Wave Xs and Bio-Tek's KC junior software (Winooski, VT). The standard range was considered as specified in the vendor's instructions. A linear regression R-square value of at least 0.95 was considered a reliable standard curve.

Assessment of executive function

Wisconsin Card Sorting Test (WCST) was examined for executive function in the current study.[13,17] WCST required strategic planning, organized searching, utilizing environmental feedback to shift cognitive sets, directing behavior toward achieving a goal, and modulating impulsive responding. WCST was commonly used in previous studies.[13,17] In addition, in order to minimize the type 1 error from multiple comparison correction, we followed the a priori findings of our previous study that a certain subset of WCST was more likely to be significant for the relationship with target biomarkers in the current study, and focused on these significant results for the correlation analyses.[18,19]

Statistical analysis

For between-group comparisons, the F-test was used for continuous variables and Pearson's test was used for categorical variables. To investigate the difference of proinflammatory cytokines (IL-6, TNF-α, and CRP) and appetite hormones (leptin, ghrelin, insulin, and adiponectin) between groups, general linear models (GLMs) with the adjustment of demographic data (age and sex), clinical symptoms (MADRS and YMRS), and BMI were performed. To assess the difference in executive function measured by WCST between groups, GLMs were examined after adjusting for demographic data, clinical symptoms, and education level. In addition, partial correlation analysis with adjustment of groups, demographic data, clinical symptoms, BMI, and education was performed to determine the association of proinflammatory cytokines and appetite hormones with executive function. A two-tailed P-value of less than .05 was considered statistically significant. All data processing and statistical analyses were performed using the SPSS version 17 software (SPSS Inc., Chicago, IL).

Results

A total of 112 young adult subjects (mean age, 26.75 years; 62.5% women) were included; the multiple-episode BD group included 38 patients, the first-episode BD group included 31 patients, and the control group included 43 healthy volunteers. Among patients with multiple-episode BD, 21 patients had >10 episodes, 4 had 5 to 10 episodes, and 13 had 2 to 4 episodes. Table 1 shows the comparison of the three groups. Patients in the multiple-episode BD group were significantly older, had lower education levels, were younger age at onset, had greater BMI, and had lower scores in MADRS and YMRS compared with the patients in the other two groups. Except for levels of CRP, TNF-α, and ghrelin, no significant differences were observed in the levels of other proinflammatory cytokines and appetite hormones among the three groups. Patients in the multiple-episode BD group had significantly higher WCST scores compared with patients in the first-episode BD group and healthy controls in terms of percent errors, percent perseverative responses, percent perseverative errors, and the number of categories completed (Table 1).

Figures 1 and 2 show the results of multivariate general linear model analysis. After adjusting for age, sex, education level, and MADRS and YMRS scores, the percent perseverative responses ($P = .044$) and percent perseverative errors ($P = .046$) significantly differed among the three groups. Post hoc analyses revealed that patients in the multiple-episode BD group had a significantly higher percent of perseverative responses on the WCST ($P = .037$)

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Table 1. Demographic Data, Proinflammatory Cytokines, and Appetite Hormones Between Patients with First-Episode and Recurrent Bipolar Disorders and Controls

	A. Recurrent bipolar disorder (n = 38)	B. First-episode bipolar disorder (n = 31)	C. Control (n = 43)	*P*-value	Post hoc
Age (years)	28.63 (3.82)	25.26 (5.39)	26.16 (4.04)	.004	A > B ~ C
Sex[a]				.065	
Male	19 (50.0)	7 (22.6)	16 (37.2)		
Female	19 (50.0)	24 (77.4)	27 (62.8)		
Education[a]				<.001	
<6 years	1 (2.6)	0 (0)	0 (0)		
6-12 years	12 (31.6)	3 (9.7)	0 (0)		
>12 years	25 (65.8)	28 (90.3)	43 (100.0)		
Age at onset (years)	20.12 (5.10)	25.07 (5.42)	–	<.001	A < B
BMI (kg/m^2)	23.98 (3.19)	21.25 (3.51)	22.15 (2.75)	.001	A > B ~ C
MADRS	8.13 (7.03)	13.39 (8.62)	0 (0)	<.001	B > A > C
YMRS	2.97 (3.69)	7.45 (7.63)	0 (0)	<.001	B > A > C
Medications (n, %)					
Lithium	7 (18.4)	2 (6.5)		.171	
Other mood stabilizers	21 (55.3)	5 (16.1)		.001	
SGA-done	14 (36.8)	19 (61.3)		.055	
SGA-pine	14 (36.8)	6 (19.4)		.182	
Cytokine levels (pg/ml)					
CRP	956.29 (1000.39)	1521.76 (2185.69)	741.66 (766.61)	.054	B > C
IL-6	34 609.39 (8131.67)	31 694.51 (8656.49)	32 491.99 (7241.40)	.281	
TNF-α	994.45 (289.89)	854.74 (224.97)	853.55 (149.74)	.010	A > B ~ C
Appetite hormones					
Insulin	7.09 (7.93)	7.94 (16.72)	6.74 (16.08)	.936	
Leptin	8215.87 (7625.72)	9688.19 (6970.03)	11 343.74 (9572.61)	.240	
Ghrelin	258.43 (185.67)	109.86 (132.21)	65.63 (81.64)	<.001	A > B ~ C
Adiponectin	6297.44 (4989.66)	8473.01 (6160.87)	9117.59 (28 869.54)	.778	
WCST					
Percent errors	25.24 (14.18)	21.87 (12.12)	16.88 (8.03)	.006	A > C
Percent perseverative responses	15.34 (15.36)	12.03 (9.52)	8.58 (3.56)	.017	A > C
Percent perseverative errors	13.55 (11.46)	10.97 (7.58)	8.26 (3.00)	.014	A > C
Number of categories completed	5.29 (1.45)	5.58 (1.36)	5.95 (0.31)	.032	A > C

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin-6; MADRS, Montgomery–Åsberg Depression Rating Scale; SGA, second-generation antipsychotics; TNF-α, tumor necrosis factor-α; WCST, Wisconsin Card Sorting Test; YMRS, Young Mania Rating Scale.
[a]Data were presented as mean (standard deviation) or count (percentage).

compared with patients in the first-episode BD group. The proportion of the percent of perseverative errors on the WCST was significantly higher in the multiple-episode BD group than in the first-episode BD group ($P = .044$) and healthy controls ($P = 0.047$; Figure 1).

After adjusting for age, sex, education level, and MADRS and YMRS scores, participants in the three groups had significantly different levels of TNF-α ($P = .014$) and ghrelin ($P < .001$) but not CRP ($P = .095$). Post hoc analyses showed that patients in the multiple-episode BD group had significantly lower levels of CRP compared with patients in the first-episode BD group ($P = .040$) and significantly higher levels of TNF-α compared with the healthy controls ($P = .003$). Additionally, ghrelin level was significantly higher in patients in the multiple-episode BD group than in patients in the first-episode BD group ($P = .002$) and healthy controls ($P < .001$); moreover, ghrelin level was significantly higher among patients in the first-episode BD group than in the healthy controls ($P = 0.030$; Figure 2). The results of partial correlation analysis demonstrated no significant association between CRP, TNF-α, or ghrelin and executive function after adjusting for age, sex, BMI, education level, and MADRS and YMRS scores (Table 2).

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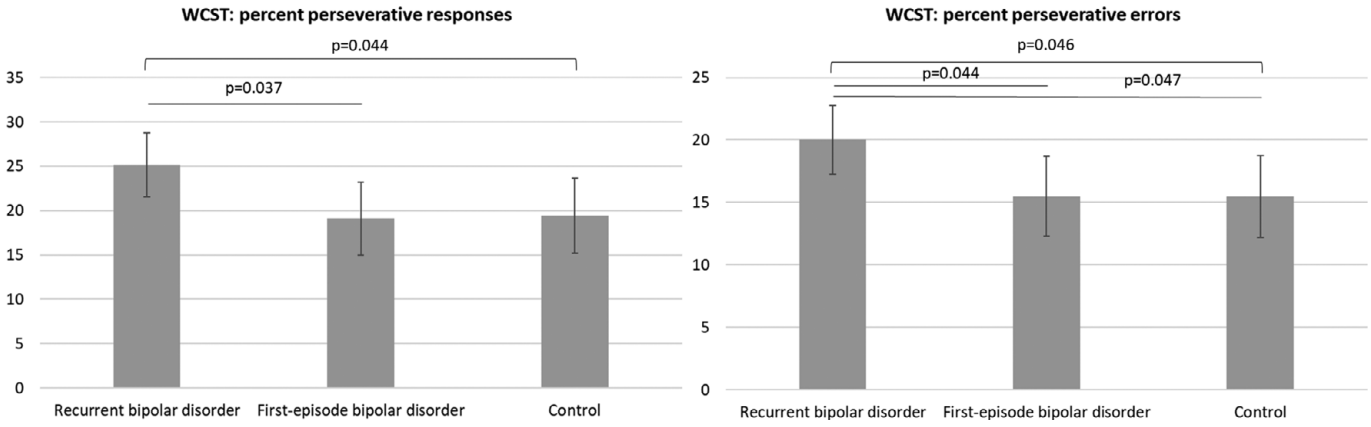

Figure 1. Cognitive function between patients with first-episode and recurrent bipolar disorders and the controls with adjustment of age, sex, education, MADRS, and YMRS. MADRS, Montgomery–Åsberg Depression Rating Scale; WCST, Wisconsin Card Sorting Test; YMRS, Young Mania Rating Scale.

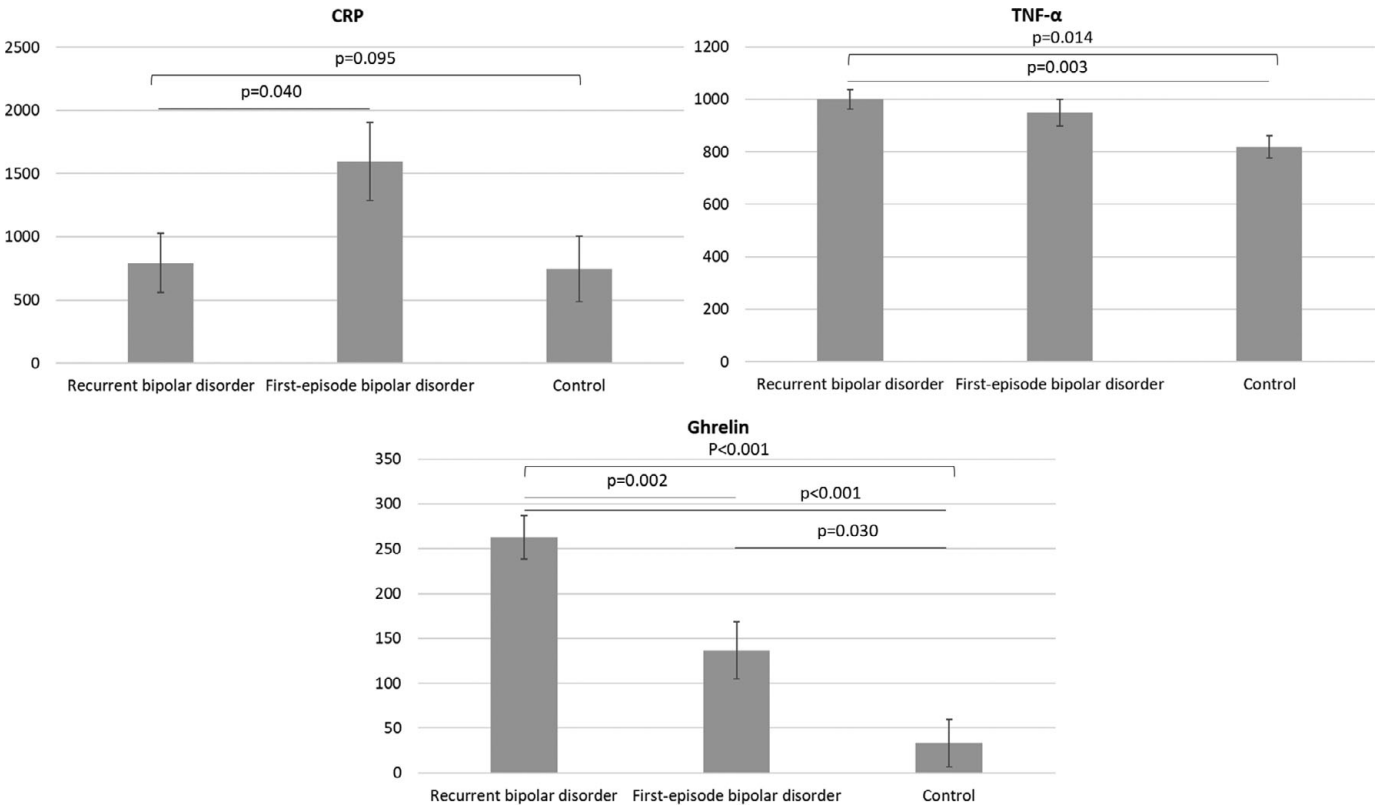

Figure 2. Levels of CRP, TNF-α, and ghrelin between patients with first-episode and recurrent bipolar disorders and the controls with adjustment of age, sex, BMI, MADRS, and YMRS. BMI, body mass index; CRP, C-reactive protein; MADRS, Montgomery–Åsberg Depression Rating Scale; TNF-α, tumor necrosis factor-α; YMRS, Young Mania Rating Scale.

Table 2. Partial Correlation of CRP, TNF-α, and Ghrelin and Cognitive Function with Adjustment of Group, Age, Sex, BMI, Education, MADRS, and YMRS

r, *P*-value	WCST: percent perseverative responses	WCST: percent perseverative errors
CRP	−0.015 (0.879)	−0.016 (0.871)
TNF-α	−0.131 (0.182)	−0.143 (0.146)
Ghrelin	−0.096 (0.332)	−0.102 (0.300)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; MADRS, Montgomery–Åsberg Depression Rating Scale; TNF-α, tumor necrosis factor-α; WCST, Wisconsin Card Sorting Test; YMRS: Young Mania Rating Scale.

Discussion

The differences between first-episode and multiple-episode BDs may represent disease progression and suggest a possible pathogenic mechanism. Through this study, we observed that patients with multiple-episode BD had significantly lower CRP levels, higher ghrelin levels, and more impaired executive function compared with patients with first-episode BD irrespective of age, sex, education level, BMI, and clinical symptoms. Additionally, no significant relationship between executive function and inflammation or appetite biomarkers was observed.

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The present study demonstrated that patients with both first-episode and multiple-episode BDs had higher TNF-α levels compared with healthy controls. Further, patients with multiple-episode BD had even higher TNF-α levels compared with patients with first-episode BD. These findings are consistent with the results of some previous reports regarding the TNF superfamily and its correlation with disease stage.[20-23] Kauer-Sant'Anna et al[23] found that TNF-α level was higher in patients with late-stage BD than in those with early-stage BD after controlling for age, sex, education level, medication, and symptoms. Both soluble TNF receptor 1[20,21] and soluble TNF receptor 2[21,22] have been reported to be positively correlated with the duration of illness in patients with BD.[20-22] Although the difference in the TNF-α levels of patients with first-episode and multiple-episode BDs did not reach statistical significance, the higher TNF-α level in patients with multiple-episode BD might be a reflection of the cumulative effect of mood episodes.[24]

Through this study, we observed that patients with BD had significantly higher ghrelin levels compared with the healthy controls and that patients with multiple-episode BD had significantly higher ghrelin levels compared with patients with first-episode BD. However, previous research has shown contradictory results regarding ghrelin levels of patients with BD. Rosso et al[25] observed that ghrelin levels were lower in patients with BD than in healthy controls, whereas Platzer et al[26] and Tunçel et al[27] reported no difference in ghrelin levels between patients with BD and healthy controls. However, Tunçel et al[27] observed that patients with BD had significantly higher ghrelin levels during euthymic episodes than during manic episodes after treatment. Thus, ghrelin likely plays a role in the pathogenesis or disease progression of BD, and altered metabolic status is commonly observed in patients with BD.[28]

Studies have reported a positive correlation between CRP levels and duration of illness.[20,29] However, in this study, we observed that only patients with first-episode BD but not those with multiple-episode BD showed elevated CRP levels. These conflicting results might be attributable to the following reasons. Although CRP is a reliable inflammatory marker, it is unlikely to reflect all inflammation pathways. This may be especially true for neuroinflammation because the CRP molecule is too large to pass through the blood–brain barrier.[30] Additionally, CRP is associated with numerous patient and disease characteristics such as BMI, age, leukocyte number, and medications.[29,31] Therefore, our results could have been affected by these potential confounders, which we did not take into consideration.

Cumulative evidence suggests that patients with BD have deficits in executive function relative to individuals without BD.[13,32] Through this study, we further determined that patients with multiple-episode BD had significantly more impaired executive function, as assessed using the WCST, compared with patients with first-episode BD, after controlling for age, sex, education level, and symptoms. These findings were similar to those of Nehra et al[6] impaired executive function might be attributable to the progressive brain damage demonstrated in neuroimaging studies.[7,33] Neither the study by Doganavsargil-Baysal et al[22] nor our study identified a relationship between WCST scores and TNF-α levels. However, Chen et al[12] reported an independent association between TNF-α and executive function, as assessed using the WCST. These conflicting findings could be explained by the different patient characteristics, episode statuses, and medications in the studies. More research is warranted to confirm the relationship, or even the interaction, between inflammation markers and cognitive function in patients with BD.

Our study has several limitations. First, the causal relationship of proinflammatory cytokines and appetite hormones with disease diagnoses could not be addressed. Second, the small sample size was the major study limitation, which may confound our results. In addition, all the enrolled patients were in a relatively stable condition and received ambulatory treatment at a single medical center, which might limit the external validity of our results. Further studies with the greater numbers of patients with BD from multiple hospitals would be necessary to validate our findings. Third, all patients with BD were allowed to continue their medications during the study. Antipsychotic medications have been reported to be associated with weight gain and a risk of metabolic disturbance.[26,28] A drug-free study may be required to confirm our results. However, keeping medications would prevent our patients from the relapse risk, which was clinically and scientifically ethical. Fourth, age differed between two BD groups, which was related to the study enrollment criteria of the first vs a recurrent episode in patients with type 1 BD. Further studies with an age-matched sample may be necessary to validate our results. Fifth, the between-group significances of TNF-α and ghrelin levels were still preserved, but the between-group significance in WCST disappeared when *P*-value was reduced from .05 to .05/3 (.0167) after the correction for multiple comparisons. The results may imply that cytokine and appetite hormone biomarkers may be more sensitive than cognitive biomarkers to differentiate a recurrent episode from the first episode in patients with type 1 BD who were relatively stable. Finally, the binary classification of the first vs a recurrent episode was arbitrary because patients with multiple-episode BD were very heterogeneous, including episode numbers and predominant polarity. To investigate the association of episode numbers with proinflammatory cytokine and appetite hormone levels and cognitive function, further studies are warranted with a large sample size.

In conclusion, patients with multiple-episode BD had significantly more impaired executive function, lower CRP levels, and higher ghrelin levels compared with patients with first-episode BD. No significant independent association of executive dysfunction with proinflammatory cytokines and appetite hormones was observed. These results underscore the importance of early diagnosis and optimal treatment of BD and need to be validated by further clinical studies.

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Author contributions. K.-L.H., M.-H.C., and Y.-M.B. designed the study and wrote the protocol and manuscripts. K.-L.H. and M.-H.C. drafted the manuscript and analyzed the data. J.-W.H. and S.-J.T. assisted with the preparation and

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proof-reading of the manuscript. M.-H.C. and Y.-M.B. provided advice on statistical analysis. All authors agreed to the submission and publication of this paper.

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