Neuropsychiatric Disease and Treatment

Dovepress
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ORIGINAL RESEARCH

Differentiations in Illness Duration, Thyroid-Stimulating Hormone, Glucose and P300 Latency Between Drug-Naïve Unipolar and Bipolar Depression: A Comparative Cross-Sectional Study

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Background: Distinguishing bipolar depression (BD) from unipolar depression (UD) remains a major clinical challenge, especially in drug-naïve patients. The present study aimed to investigate whether demographic, clinical, and biochemical parameters can help differentiate drug-naïve BD from UD.

Methods: Drug-naïve patients with UD and BD were recruited from Shandong Mental Health Center. Ninety-four inpatients (61 UD and 33 BD) were assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17) and P300 latency. Fasting serum levels of free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), as well as fasting plasma glucose (FPG), lipid, C-reactive protein (CRP), and uric acid (UA) indicators were measured.

Results: Patients with BD had longer illness duration and P300 latency and lower FT3 levels, but higher levels of TSH and FPG than patients with UD (all $P<0.05$). Binary logistic regression analysis indicated illness duration, TSH, FPG, and P300 latency were significantly associated with BD. Illness duration, TSH, FPG, and P300 latency achieved an area under the ROC curve of 0.777, 0.699, 0.646, and 0.635, respectively, in discriminating unipolar and bipolar depression.

Conclusion: Increased illness duration, serum TSH and FPG levels, and P300 latency were independent risk factors for BD. Demographic, clinical, biochemical, and electrophysiological markers identified may have the potential to distinguish BD from UD.

Keywords: unipolar depression, bipolar depression, illness duration, thyroid-stimulating hormone, fasting plasma glucose, P300

Introduction

Bipolar disorder (BPD) and major depressive disorder (MDD) affect approximately 2.4% and 16.2% of the global population, respectively.[1,2] Both are leading causes of high global burden, disability, suicide, and cognitive deficit.[3–7] The depressive episodes in BPD are largely clinically similar to those seen in unipolar depression (UD).[8] Although mania and hypomania are the signature characteristics of BPD, depressive episodes have a higher prevalence during the illness duration.[4] In addition, patients with BPD who exhibit subthreshold symptoms of mania and hypomania tend to display

Received: 13 September 2024
Accepted: 7 January 2025
Published: 29 January 2025

creativity in their daily work and studies,[9,10] and are much more likely to seek clinical assistance when experiencing depressive episodes.[11] Various factors make it difficult to correctly distinguish bipolar depression (BD) from UD in clinical conditions.

Thyroid hormones play a critical role in brain functionality. Triiodothyronine and levothyroxine were used as adjunctive agents in affective disorders for over 50 years,[12,13] which arose from observed associations between psychiatric symptoms and thyroid disease states. Neuropsychiatric symptoms associated with thyroid dysfunction resolve quickly when returning to a euthyroid state.[14,15] Thyroid hormones have the potential to modulate the phenotypic expression of major affective disorders.[16] Indeed, hypothyroidism has recently been positively associated with an increased risk of MDD and BPD.[17] Thyroid hormone variations, even within the normal range, may be associated with a risk of psychiatric disorders, though the mechanism remains unclear.

Metabolic syndrome is a group of risk factors including obesity, high blood pressure, and dysregulation of lipids and glucose.[18] Patients with MDD and BPD have a higher risk for metabolic syndrome compared with the healthy population.[19,20] Although the exact pathophysiology of this association is unclear, several potential factors contribute to the risk phenotypes, including a diet high in sugar and fat, obesity, heritability, inflammation, and oxidative stress.[21–24] The widespread use of antipsychotics in patients with affective disorders further increases the risk of metabolic syndrome.[25,26]

P300 is a widely studied component of event-related evoked potential, which has been closely associated with cognitive function, including memory, attention, and executive function.[27] As a nerve electrophysiological indicator, P300 has considerable advantages, including non-invasiveness, affordability, convenience, and high temporal resolution.[28,29] The characteristics of P300 in UD and BD include increased P300 latencies and decreased P300 amplitudes compared to healthy controls. A recent meta-analysis discovered that BD patients have longer P300 latency than UD patients during both periods of acute episode and remission.[30] Moreover, P300 latency decreased to normal in remitted UD patients, but not remitted BD patients.[30] Hence, P300 latency has the potential to differentiate BD from UD.

Considering the complex mechanisms and identification difficulty of BPD, demographic and clinical data, common blood biochemical indices, and event-related potentials were used to differentiate drug-naïve patients with BD from UD. The results of this study may provide psychiatrists with a multi-dimensional perspective based on readily available information of inpatients to identify differences between UD and BD in the early stage.

Methods

Study Patients

All patients were consecutively recruited between December 2019 and June 2022 in Shandong Mental Health Center, a large psychiatric hospital with over 1000 hospital beds in Jinan, China. The ethics committee of Shandong Mental Health Center approved the study (2019-R33). The protocols for human experiments were conducted in accordance with the Declaration of Helsinki. All patients received a comprehensive explanation of the study and signed an informed written consent before inclusion.

Inclusion criteria included: (1) aged 16–50 years; (2) Han Chinese; (3) Junior high school level or above, with sufficient ability to understand and complete study assessments; (4) diagnosed with major depressive disorder or bipolar I or II disorder according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (DSM-IV-TR) criteria, with a current depressive episode, ie UD and BD; (5) had not received any psychotropic medication or psychotherapy; (6) score of the 17-item Hamilton Depression Rating Scale (HAMD-17) $\geq$17.

Exclusion criteria were: (1) BD with mixed state or with rapid cycling; (2) comorbid with other psychiatric disorders; (3) breastfeeding, pregnant or intended pregnancy; (4) physical diseases such as thyroid-related diseases (including subclinical conditions), hyperlipidemia, diabetes, gout, immune diseases and other serious medical conditions (eg severe heart, brain, liver, and hematological diseases).

Biochemical Measurements

Fasting venous blood samples of 5 mL were collected from all patients between 7:00 am and 7:30 am on the day following admission to the hospital. The blood was centrifuged at 3000 g for 10 minutes at 4°C, and the resulting serum was withdrawn and analyzed immediately. Peripheral thyroid levels of FT4, FT3, and TSH were measured using an Architect i2000sr immunoassay analyzer (Abbott Laboratories; Lake Bluff, IL, USA), employing a chemiluminescent immunoassay method, following the manufacturer's protocols. This method ensures high sensitivity and reproducibility. Serum levels of triglycerides (TG), cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, fasting plasma glucose, and UA were measured using a Cobas C702 automatic biochemical analyzer (Roche, Basel, Switzerland), which utilizes colorimetric and enzymatic methods based on established protocols for each biomarker. CRP level was measured using an enhanced immunoturbidimetric method, in accordance with the manufacturer's instructions, which ensures reliable and accurate quantification. Quality control was maintained through regular calibration, reagent verification, and internal quality sample testing. All blood samples were assayed by the same technician, who was blind to the sample clinical information.

P300 Measurement

The oddball paradigm was used to determine all P300 measurements and included two different tones, a 2000 Hz target and a 1000 Hz non-target stimulus. The auditory stimuli were presented randomly, with target tones of 2000 Hz appearing 20% of the time and standard tones of 1000 Hz appearing 80% of the time, at a rate of 0.5 Hz. The stimuli were presented at 70 dB. The participants were instructed to sit with their eyes closed and focus their attention on mentally counting the target stimulation. Electrodes were placed according to the instructions of the 10–20 standard international position system. P300 potential latency was measured at the wave peak with the most prominent positive wave between 250–800 ms. The P300 measurement procedure was standardized across all participants, each of whom was tested under the same room conditions, and had a standardized rest period prior to the test to minimize any external variables that might affect the P300 latency results.

Statistical Analysis

IBM SPSS Statistics Version 24 for Windows (IBM, Armonk, NY, USA) and GraphPad Prism 9 were used for statistical analyses. All the continuous variables were inspected for normality by the Kolmogorov–Smirnov test. Normally distributed continuous data are presented as means and standard deviation, non-normally-distributed continuous data are presented as medians and interquartile ranges, and categorical data are expressed as raw numbers and percentages. The chi-square test was conducted to exam group differences in categorical variables. For the comparison of the continuous variables between groups, we used independent sample *t*-tests for parametric variables and the Mann–Whitney *U*-tests for non-parametric variables. In addition, FT3, TSH, and FPG levels, and P300 latency were compared between groups using analysis of covariance (ANCOVA) to control for potentially confounding variables that significantly differed between groups in univariate analyses. A binary logistic regression model was used for the multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. Receiver operating characteristic (ROC) analysis was used to show the role of illness duration, TSH, FPG, and P300 latency in differentiating unipolar and bipolar depression.

Results

Demographic and Clinical Characteristics

Sixty-one participants in the UD group and 33 participants in the BD group were included in the study. The demographic and clinical characteristics of the two groups are presented in Table 1. There was no significant difference in demographic characteristics between the two groups, including age ($Z=-1.298$, $P=0.194$), gender ($X^2=0.452$, $P=0.501$), education ($Z=-0.820$, $P=0.412$), and BMI ($t=-1.148$, $P=0.254$). Compared with UD, patients with BD presented longer illness duration ($Z=-4.437$, $P<0.001$) and P300 latency ($Z=-2.155$, $P=0.031$). There were no significant differences between the UD group and the BD group in age of onset, family history of mental illness, and HADM-17 (all

Table 1 Demographic and Clinical Details of Recruited Subjects in the Study

Characteristics	Unipolar Depression (n=61)	Bipolar Depression (n=33)	$t/X^2/Z$	*P*
Age (years)	22 (18, 33)	27 (19, 36)	−1.298	0.194
Gender	34 (55.7%)	16 (48.5%)	0.452	0.501
Male	27 (44.3%)	17 (51.5%)		
Female				
Education (years)	12 (10, 16)	12 (10, 12)	−0.820	0.412
BMI	23.27 ± 3.75	24.27 ± 4.48	−1.148	0.254
Age of onset (years)	17 (16, 32)	21 (15, 26)	−0.060	0.953
Illness duration (years)	2.00 (0.79, 5.00)	6.00 (3.67, 9.00)	−4.437	<0.001
Family history of mental illness	12 (19.7%)	10 (30.3%)	1.350	0.245
Yes	49 (80.3%)	23 (69.7%)		
No				
HAMD-17	24.69 ± 3.75	25.67 ± 5.19	−0.968	0.338
P300 latency (ms)	312 (292, 375)	356 (304, 395)	−2.155	0.031

Abbreviations: BMI, body mass index; HAMD-17, 17 item Hamilton Depression Rating Scale.

P>0.05). After adjusting for illness duration, ANCOVA revealed that P300 latency remained significantly higher in the BD group compared to the UD group (F= 4.831, *P* = 0.030).

Comparison of Biochemical Indices

Routine biochemical indices including FT3, FT4, TSH, TG, total cholesterol (CHO), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), FPG, CRP and UA were analyzed, and significant differences were found only in the serum levels of FT3, TSH, and FPG (Table 2). Serum FT3 levels were significantly lower in patients with BD than in patients with UD (Z=−2.103, *P*=0.035), whereas serum TSH levels (Z=−3.181, *P*=0.001) and serum FPG levels (Z=2.333, *P*=0.020) were significantly higher. ANCOVA demonstrated that serum TSH and FPG remained significantly higher in the BD group (F=14.012, *P*<0.001) over the UD group (F=4.702, *P*=0.033) after adjusting for illness duration. However, there was no significant difference in FT3 level between the two groups after adjusting for the confounding variable (F=1.818, *P*=0.181).

Table 2 Biochemical Indices of Blood Serum of Patients With Unipolar and Bipolar Depression

	Unipolar Depression (n=61)	Bipolar Depression (n=33)	t/Z	*P*
FT3 (pg/mL)	2.89 (2.63, 3.08)	2.68 (2.35, 3.02)	−2.103	0.035
FT4 (ng/dL)	0.94 (0.84, 1.06)	0.93 (0.83, 1.13)	−0.345	0.730
TSH (μIU/mL)	1.95 (1.25, 3.03)	3.17 (1.92, 5.07)	−3.181	0.001
TG (mmol/L)	0.99 (0.74, 1.48)	1.15 (0.76, 1.70)	−0.765	0.445
CHO (mmol/L)	4.16 (3.72, 4.89)	4.35 (4.03, 4.92)	−1.038	0.299
HDL-C (mmol/L)	1.24 ± 0.24	1.23 ± 0.25	0.125	0.900
LDL-C (mmol/L)	2.32 (1.98, 2.93)	2.43 (2.22, 3.04)	−1.311	0.190
FPG (mmol/L)	4.30 (4.00, 4.50)	4.40 (4.20, 5.05)	−2.333	0.020
CRP (mg/L)	0.31 (0.03, 1.82)	0.52 (0.06, 2.20)	−0.923	0.356
UA (μmol/L)	355.88 ±102.73	339.88 ± 98.69	0.728	0.468

Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TG, triglycerides; CHO, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FPG, fasting plasma glucose; CRP, C-reactive protein; UA, uric acid.

Table 3 Logistic Regression Analysis of Factors Associated With Bipolar Depression

Variables	B	S.E.	Wald	*P* value	OR (95% CI)
Illness duration	0.213	0.077	7.617	0.006	1.238 (1.064–1.440)
TSH	0.632	0.212	8.866	0.003	1.881 (1.241–2.852)
FPG	1.205	0.574	4.408	0.036	3.335 (1.083, 10.268)
P300 latency	0.010	0.004	5.283	0.022	1.010 (1.001–1.019)

Notes: B, regression coefficient; S.E, standard error; OR, odds ratio.
Abbreviations: TSH, thyroid-stimulating hormone; FPG, fasting plasma glucose.

Table 4 The Results of ROC Analysis

Measure	Cut-Off Value	AUC	95% CI	Sensitivity	Specificity
Illness duration	3.167 years	0.777	0.681–0.873	78.8%	67.2%
TSH	2.680 μIU/mL	0.699	0.587–0.812	60.6%	72.1%
FPG	4.550 mmol/L	0.646	0.526–0.765	48.5%	77.0%
P300 latency	323 ms	0.635	0.522–0.749	63.6%	62.3%

Abbreviations: TSH, thyroid-stimulating hormone; FPG, fasting plasma glucose.

Factors in Differentiating Unipolar and Bipolar Depression

Significant independent variables from the comparison between unipolar and bipolar depression including illness duration, FT3, TSH, FPG, and P300 latency were used in the binary logistic regression analysis (Table 3). Multivariate regression analysis revealed that increased illness duration (OR = 1.238, 95% CI = 1.064–1.440, P = 0.006), TSH (OR = 1.881, 95% CI = 1.241–2.852, P = 0.003) and FPG (OR = 3.335, 95% CI = 1.083–10.268, P = 0.036) levels, and P300 latency (OR = 1.010, 95% CI = 1.001–1.019, P = 0.022) were independently associated with bipolar depression.

Receiver Operating Characteristics (ROC) for Illness Duration, TSH, FPG, and P300 Latency for the Diagnosis of Bipolar Depression

ROC analysis helped to determine the cut-off values for illness duration, TSH level, FPG level, and P300 latency needed to predict patients with BD (Table 4 and Figure 1). The cut-off values can help clinicians more accurately differentiate between BD and UD, potentially leading to earlier diagnosis and more targeted treatments. According to ROC analysis,

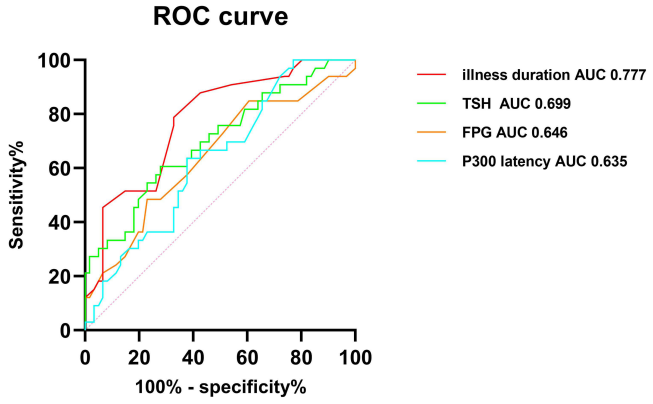

Figure 1 Receiver operating characteristic (ROC) curve for the diagnostic ability of illness duration, TSH, FPG, and P300 latency (Bipolar depression vs Unipolar depression). Illness duration: AUC 0.777 (95% CI: 0.681–0.873), P <0.001; TSH: AUC 0.699 (95% CI: 0.587–0.812), P =0.002; FPG: AUC 0.646 (95% CI: 0.526–0.765), P =0.020; P300 latency: AUC 0.635 (95% CI: 0.522–0.749), P =0.031.
Note: AUC, area under the ROC curve.

https://doi.org/10.2147/NDT.S496172

the cut-off value of illness duration to predict BD patients was 3.167 years, with an area under the curve (AUC) of 0.777 (95% CI: 0.681–0.873), a sensitivity of 78.8%, and a specificity of 67.2%. The cut-off value of TSH to predict BD patients was 2.680 μIU/mL, with an AUC of 0.699 (95% CI: 0.587–0.812), a sensitivity of 60.6%, and a specificity of 72.1%. The cut-off value of FPG to predict BD patients was 4.55 mmol/L, with an AUC of 0.646 (95% CI: 0.526–0.765), a sensitivity of 48.5%, and a specificity of 77.0%. The cut-off value of P300 latency to predict BD patients was 323 ms, with an AUC of 0.635 (95% CI: 0.522–0.749), a sensitivity of 63.6%, and a specificity of 62.3%.

Discussion

Previous studies have indicated reduced peripheral brain-derived neurotrophic factor levels across various affective states, including MDD, bipolar I and II disorders, regardless of comorbid conditions or treatment status.[31] The current results add to this literature and indicate that specific clinical characteristics, blood biochemical indices, and P300 latency may help to distinguish between drug-naïve BD and UD patients. Notably, patients with BD had significantly higher serum levels of TSH and FPG than patients with UD. These results could indicate a possible dysfunction of the hypothalamus-pituitary-thyroid (HPT) axis and glucose metabolism in drug-naïve patients with BD. In this study, we also found longer illness duration and P300 latency were risk factors for BD, which is consistent with the results of previous studies.[30,32]

Our comparative cross-sectional study showed that drug-naïve BD patients had a lower FT3 concentration and a higher TSH concentration than drug-naïve UD patients in univariate analysis. Triiodothyronine, high-dose thyroxine, and L-thyroxine have proved to be effective as an augmentation in severely therapy-resistant affective disorders for a long time.[33–35] Electroconvulsive therapy and psychiatric medication can disrupt the activity of the HPT axis, leading to dysfunction of thyroid hormones.[36–38] To avoid the effects of psychiatric therapy on the thyroid hormones, drug-naïve patients with UD and BD were recruited. A previous study reported that unmedicated BD patients had lower triiodothyronine and FT3 levels compared to UD patients.[39] Furthermore, Caucasian patients with BD had a higher TSH levels than UD.[40] A systematic analysis of multiple phenotypic and genotypic databases revealed a positive correlation between hypothyroidism and an increased risk of MDD and BPD.[17] A Mendelian randomization study found that a lower level of FT4, but not FT3 or TSH, is associated with an increased risk of BPD.[41] However, our logistic regression analysis found that increased TSH concentration was a risk factor for BD. One potential explanation for this apparent discrepancy is that the origins of the population are distinct. The GWAS data is of European ancestry, whereas our study is of East Asian ancestry. The differences in genetic architecture of diverse ancestries may affect TSH concentration. Additionally, the sample groups in the GWAS data consist of BPD and healthy controls, while we recruited drug-naïve BD and UD patients. In brief, thyroid hormones could potentially play a role in differentiating drug-naïve patients with BD from UD.

We also found that serum FPG in drug-naïve BD patients was significantly higher than drug-naïve UD patients, suggesting that FPG may be an independent risk factor for BD. Interestingly, an early study revealed that drug-free BD patients had significantly lower supratentorial whole-brain glucose metabolic rate than UD,[42] while another showed that drug-free UD patients had significantly greater resistance to insulin-induced hypoglycemia than BD.[43] Higher cerebrospinal fluid glucose has also been associated with depressive symptoms,[44] as well as glucose metabolism, lipid metabolism, inflammation,[45,46] and UA metabolism.[47] Furthermore, the prevalence of hypertriglyceridemia, hypertension, and elevated FPG observed in BPD were higher than in the general population.[48] Glucose is well known for providing energy, and energy fluctuations are consistent with mood swings in BPD. Hence, further research is needed to determine whether pathways of glucose metabolism may be suitable biomarkers for distinguishing BD from UD.

Our study showed that illness duration in drug-naïve BD patients was longer than UD, consistent with previous studies.[32,49] Because the first episode of BPD, characterized by mania or hypomania, is often energetic and productive, patients may not seek clinical help until depression develops. A previous study proposed illness duration was inversely correlated with total gray matter volume in patients with BPD but not in UD,[50] which suggests progression of illness in BPD may contribute to abnormal cellular plasticity. Using logistic analysis, we found that longer illness duration was a risk factor for BD, which may aid psychiatrists differentiate drug-naïve BD patients from UD as they treat patients with unique demographics and clinical characteristics. Earlier identification of BPD is critical to the prognosis of the disease.

Finally, P300 latency in drug-naïve BD patients was significantly longer than UD, and longer P300 latency was an independent risk factor for BD. Several studies have previously reported significantly lower P300 amplitude and prolonged P300 latency in BPD and UD relative to those in normal controls,[30,51,52] and a meta-analysis proposed patients with BD had longer P300 latency than UD in both acute episodes and remissions.[30] After remission, P300 latency decreased significantly in both BD and UD patients, but only in remitted UD patients returned to normal levels.[30] The findings are consistent with a widely accepted view of cognitive impairment persisting in BD. P300 latency reflects neural speed or brain efficiency.[27] The difference in P300 latency between BD and UD during both acute episodes and remissions may indicate slower neural speed or reduced brain efficiency in evaluating or categorizing stimuli in BD patients. BD shows more widespread abnormalities in white matter connectivity and white matter hyperintensities compared to UD.[53] In addition, BD shows different patterns of functional abnormalities in emotion regulation and attention control neural circuits, which may contribute to the neurobiological basis of the relatively long P300 latency in BD.[53] The change in P300 is not specific to BD and also found in schizophrenia, epilepsy, mild cognitive impairment, and alcohol use disorder.[52,54–56] Nevertheless, P300 latency still has the potential to be an auxiliary diagnostic marker for differentiating BD from UD.

ROC curves were constructed to determine optimal cut-off values of illness duration, TSH, FPG, and P300 latency for the diagnosis of BD, which have not yet been identified. As identified earlier, these characteristics may be used to support the diagnosis of BD. The identification of BD indeed remains a significant clinical challenge, and its complexity often prevents clinicians from distinguishing BD from UD. While research in brain imaging, genomics, proteomics, and metabolomics has provided valuable insights into the underlying mechanisms of BD, these advanced techniques are technically demanding and not readily accessible in routine clinical practice. In contrast, our study focuses on biologically relevant and clinically feasible indicators, such as demographic data, non-invasive electrophysiological markers, and biochemical markers. We believe that combining P300 latency with specific biochemical markers (such as TSH, FPG) and demographic factors (eg, illness duration) offers a more prominent and accessible means of differentiating BD from UD. This multidimensional approach allows clinicians to more effectively distinguish BD from UD, providing a valuable tool for clinical diagnosis and early intervention.

There were several limitations to the current study. First, this was a cross-sectional study that did not explore causality. Second, the sample size in our study was small and further research with larger sample sizes is needed to validate the current findings. Third, the sample was from a single center in East Asia, and further studies in diverse populations are needed to validate the results. Finally, although disease states for BD and UD patients were identified by experienced psychiatrists, drug-naïve UD patients do have the potential to develop BPD in the future. Hence, follow-up of these samples could help improve the accuracy of our study.

Conclusions

Increased illness duration, serum TSH and FPG levels, and P300 latency may be risk factors for BD. Our study identified P300 latency and specific biochemical markers (eg, TSH, FPG) as potential differentiators between UD and BD in drug-naïve patients. These findings may help clinicians distinguish BD from UD and provide a multidimensional perspective for clinicians and patients to better understand the characteristics of affective disorders.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Statement

This study was approved by the Ethics Committee of Shandong Mental Health Center approved the study (2019-R33). The protocols for human experiments were conducted in accordance with the Declaration of Helsinki. All patients signed written informed consent before inclusion.

Acknowledgments

We sincerely thank all the participants of this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by grants from the National Natural Science Foundation of China (Nos. 81871052 and 81701326) to Chuanjun Zhuo.

Disclosure

All authors declare that there are no potential conflicts of interest for this work.

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