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Original Article

CpG methylation of brain-derived the neurotrophic factor gene promoter as a potent diagnostic and prognostic biomarker for post-traumatic stress disorder

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Abstract: Posttraumatic stress disorder (PTSD) is a common response to traumatic events. Many PTSD patients recover in the next few months, but in a significant subgroup, the symptoms persist, often for years. The present study shows that brain-derived neurotrophic factor (BDNF) gene is related to the pathological mechanism of a variety of mental diseases. Here we investigate the effect of methylation of BDNF gene and different loci on the occurrence and development of PTSD. Initially, using case-control method, 322 PTSD patients as well as 215 normal controls were selected as the subjects. Following peripheral venous blood being collected from the subjects, genomic DNA was extracted. Methylation of the cytosine-guanine dinucleotide (CpG) island in BDNF gene promoter was then modified by bisulfite and detected through direct sequencing. Methylation of CpG in BDNF gene promoter was closely related to PTSD, and the methylation level of CpG in BDNF gene promoter may serve as a biomarker for PTSD diagnosis. Types of trauma of PTSD patients may have a certain effect on the methylation level of BDNF gene promoter. Methylation level of the BDNF promoter, depressive degree score, poor sleep quality score, early trauma score, mental stress score, and trauma type were closely related to the occurrence and development of PTSD. Taken together, our data support the notion that stressful life events may directly cause CpG methylation in the BDNF promoter of PTSD patients. Stress types may be associated with methylation levels of CpG1, CpG7, and CpG18 in the BDNF promoter of PTSD patients. These findings provide a new way for the diagnosis and treatment of PTSD.

Keywords: Brain-derived neurotrophic factor, DNA methylation, posttraumatic stress disorder, epigenetic inheritance

Introduction

Post-traumatic stress disorder (PTSD) primarily develops following exposure to life-threatening traumatic experiences and has been widely studied as typical case of stress related mental disorders [1]. Car accident, sexual assault, physical attack, combat exposure, survival of natural disasters, or other potential trauma cases may result in the diagnosis of PTSD [2]. PTSD patients suffer from symptoms for many years, such as re-experiencing of traumatic events, enhanced arousal, and avoidance/numbing [3]. A meta-analysis of suicide psychiatric diagnoses research on high-risk populations reported that PTSD patients have extremely high suicide rates [4], in addition to other related research [5, 6]. The current treatment methods for PTSD mainly consist of antidepressant medications and psychotherapy, but they are still not very effective, considering drug use disorders, general medical diseases, and suicide [7]. Dysregulation of brain-derived neurotrophic factor (BDNF) has been found under the conditions of traumatic brain injury (TBI) and PTSD [8]. The induction of BDNF together with the activation of its intracellular receptors functions in engendering nerve reconnection, regeneration, and dendrite buds, and enhancing synaptic effectiveness [9].

As a member of the neurotrophic family of polypeptide growth factors, BDNF is widely found in the brain of developmental and adult mammals

considered to be a key regulator of the development of neurons in the central nervous system [10]. BDNF has also been proven to be involved in the development and treatment of many psychiatric disorders in recent years [11, 12]. In addition, BDNF is considered to be an important factor mediating synaptic plasticity, which plays a crucial role in learning and memory process, especially in the consolidation and retreat of the memory of fear [13]. At the molecular level, BDNF Val66Met polymorphism may correlate with PTSD risk, severity of PTSD symptoms, psychiatric symptoms in PTSD, and response to exposure therapy for PTSD, proving that BDNF may be associated with a potential mechanism of abnormal learning and memory processes in PTSD [14]. The aim of this controlled study was to explore clinical correlations of BDNF in a population showing PTSD symptomatology. This study explored the possible pathogenesis of PTSD from the perspective of molecular biology, and the possible pathways of life events affecting the pathogenesis of PTSD. It further explored the etiology and pathogenesis of PTSD, so as to provide a theoretical basis for PTSD early diagnosis, early intervention, and individualized treatment, and even reference for the prevention of PTSD.

Methods and materials

Ethic statement

This study was approved by the Ethics Committee of Hainan General Hospital. Written informed consent was obtained from all patients.

Study subjects and clinical evaluation

A total of 322 PTSD patients were selected from the epidemiological survey acting in Hainan General Hospital from August 2012 to March 2016. All the patients underwent clinical examination and tested using PTSD coping-adaptation processing scale (CAPS) in accord with the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). They were diagnosed by two psychiatrists (at least one with senior professional title). Exclusion criteria are shown as follows: (1) Patients with physical diseases that can cause impairment of cognitive function; (2) Patients who had taken drugs affecting cognitive function during the last three months; (3) Patients with obvious mental retardation. Another 215 healthy people who had done physical examination in Hainan General Hospital during the same period were selected as controls. There was no difference between the PTSD group and the control group in age, sex composition, national composition, and education level ($p < 0.05$).

All patients filled in basic information into the survey form and completed the following assessment scales: Post traumatic Stress Checklist (self-assessment of the severity of PTSD), Beck Depression Inventory (assessment of the degree of depression), Pittsburgh Sleep Quality Index (evaluation of sleep quality), Early Trauma Inventory (assessment of childhood traumatic stimulation), and Symptom Checklist-90-R (estimation of mental stress).

Methylation detection

After the epidemiological investigation and assessment scales, samples (5~10 mL each) of anterior elbow vein blood were taken from the study subjects, anti-coagulated by ethylenediamine tetraacetic acid (EDTA) and sent to the Central Laboratory in Hainan General Hospitals frozen at -20°C. Genomic DNA was extracted from the whole-blood samples by centrifuge column method using DNA Extraction Kit (Omega Bio-Tek, Inc., Norcross, GA, USA). The determination of concentration and purity conformed to the requirements of PCR amplification. Successively, we detected DNA methylation of BDNF gene.

Online software CpGplot (http://emboss.bioinformatics.nl/cgi-bin/emboss/CpGplot) was used to predict the CpG island. PCR amplified the 297 bp DNA fragment of CpG island in promoter IV of BDNF gene (forward primer: CCCTGGAACGGAACTCTTCT; reverse primer: ATTGCATGGCGGAGGTAATA). SNaPshot Multiplex Kit (Applied Biosystems, Foster City, CA, USA) was employed for multilocus methylation-specific single nucleotide primer extension (MS-SNuPE) at 19 CpG loci in the CpG Island. The primers used were shown as follows: CCTGGAACGGAACTCTTCTAATAAAAGATGTATCATTTTAAATGCGCTGAATTTTGATTCTGTAATTTCGGCACTAGAGTGTCTATTTCGAGGCAGCGGAGGTATCATATGACAGCGCACGCACGTCAGGCACCGTGGAGCTCCCACCCACTTTCCCATTCACCGCGGAGAGGGCTGCCTCGCTGCCGCTCCCCCCGGCGAACTAGCATGAAATCTCCCTGCCTCTGCCGAGATCAAATGAGCTTCTCGCTGATGGGGTGCGAGATTACCTCCGCCATGCAAT (the underlined are CpG dinucleotide loci). The reaction system were shown as follows: 4 μL template DNA, 0.8 μL forward primers, 0.8 μL

Table 1. Comparison of general information between the PTSD and control groups

Characteristics	PTSD (n = 322) (A)	High trauma (n = 145) (B)	Low Trauma (n = 177) (C)	Control (n = 215) (D)	*p* (A vs. D)	*p* (B vs. C)
	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %		
Age (years)	39.25 ± 7.16	39.81 ± 7.09	38.79 ± 7.20	38.68 ± 7.02	0.339	0.213
Gender (% female)	61.18%	57.14%	64.41%	55.81%	0.215	0.189
BMI	30.51 ± 4.67	28.07 ± 4.23	30.87 ± 4.98	30.02 ± 4.66	0.234	0.126
Ethnicity (% Han ethnicity)	96.58%	97.24%	96.05%	98.14%	0.284	0.557
Education years	12.97 ± 3.35	12.76 ± 3.59	13.15 ± 3.14	13.09 ± 2.72	0.712	0.422
History of Drinking	81.06%	80.00%	81.92%	77.21%	0.279	0.662
History of Smoking	61.80%	61.38%	62.15%	54.42%	0.090	0.909
PTSD Severity (Clinician-rated)	68.78 ± 16.65	76.35 ± 17.58	62.57 ± 12.91	3.52 ± 0.97	< 0.001	< 0.001
PTSD Severity (Self-reported)	60.45 ± 12.48	67.20 ± 12.15	54.92 ± 9.75	22.94 ± 4.91	< 0.001	< 0.001
Depression Severity	26.71 ± 7.34	31.31 ± 7.75	22.95 ± 4.17	4.72 ± 1.13	< 0.001	< 0.001
Poor Sleep Quality	12.94 ± 4.03	14.87 ± 4.12	11.36 ± 3.18	6.36 ± 1.88	< 0.001	< 0.001
Early Trauma Exposure	6.52 ± 2.10	7.75 ± 2.32	5.52 ± 1.19	5.54 ± 1.07	< 0.001	< 0.001
Psychiatric Distress	2.34 ± 0.77	2.84 ± 0.77	1.93 ± 0.46	1.12 ± 0.26	< 0.001	< 0.001

Note: BMI, body mass index; PTSD, posttraumatic stress disorder, SD, standard deviation. The measurement data was presented as mean ± standard deviation. Enumeration data are expressed as percentage or frequency and analyzed by *Chi*-square test. Comparisons between two groups were analyzed using *t*-tests.

reverse primers, 10 μL Mix, with the addition of double-distilled water (ddH_2O) to a total volume of 20 μL. The reaction condition was shown as follows: pre-degeneration at 95°C for 3 min, and 45 cycles of denaturation at 95°C for 30 s, annealing at 58.5°C for 1 min, and extension at 72°C for 45 s, followed by a last extension at 72°C for 5 min and termination at 4°C. After that, 15 μL PCR product was sent to a company (Shanghai Sangon Biological Engineering Technology & Services Co., Ltd., Shanghai, China) for sequencing.

Statistical analysis

The obtained data were inputted by Epidata3.1 software and analyzed by SPSS 21.0 (IBM Corp., Armonk, NY, USA). The measurement data were presented as mean ± standard deviation. Enumeration data were expressed as percentage or frequency and analyzed by Chi-square test. Comparisons between two groups were analyzed using t-tests. Spearman correlation analysis between types of trauma and BDNF methylation was performed. A $p < 0.05$ was considered statistically significant.

Results

Comparisons of baseline characteristics of study subjects

The general information of PTSD and control patients is shown in **Table 1**. There were no significant differences in age, sex composition, body mass index (BMI), ethnic composition, education levels, drinking history, and smoking history between the two groups ($p > 0.05$). Compared with the control group, the PTSD group showed an increase in the PTSD severity score (clinical assessment), PTSD severity score (self-assessment), depression degree score, poor sleep quality score, early trauma stimulation score, and mental stress score ($p < 0.05$).

According to the results of the clinical and self-assessment PTSD severity score, subgrouping was done into a high trauma group (N = 145; PTSD severity [Clinician-rated] = 76.35 ± 17.58; PTSD severity [Self-reported] = 67.20 ± 12.15) and a low trauma group (N = 177; PTSD severity [Clinician-rated] = 62.57 ± 12.91; PTSD severity [Self-Reported] = 54.92 ± 9.75). In comparison to the high trauma group, the depression degree score, poor sleep quality score, early traumatic stimulation score and mental stress score in the low trauma group were all decreased ($p < 0.05$).

Methylation level of CpG in BDNF gene promoter may serve as a biomarker for the diagnosis of PTSD

To investigate the relationship between methylation of BDNF and PTSD, the methylation levels of CpG in BDNF gene promoter were detected. The results showed that no significant differences in the level of methylation of CpG8,

Table 2. Comparison of methylation of BDNF in PTSD and control groups

Locus	PTSD (n = 322)	Control (n = 215)	*t*	*p*	High trauma (n = 145)	Low trauma (n = 177)	*t*	*p*
	Mean ± SD	Mean ± SD			Mean ± SD	Mean ± SD		
CpG1	3.13 ± 1.04	8.39 ± 0.99	58.54	< 0.001	2.05 ± 0.34	4.02 ± 1.49	52.57	< 0.001
CpG2	4.07 ± 1.48	14.49 ± 2.59	59.17	< 0.001	3.88 ± 1.44	4.23 ± 1.49	2.13	0.034
CpG3	2.02 ± 1.41	4.59 ± 0.89	23.75	< 0.001	0.51 ± 0.11	3.25 ± 0.44	73.12	< 0.001
CpG4	1.75 ± 0.80	3.89 ± 0.85	29.62	< 0.001	1.03 ± 0.21	2.34 ± 0.59	25.44	< 0.001
CpG5	0.83 ± 0.29	5.67 ± 1.64	51.78	< 0.001	0.65 ± 0.19	0.98 ± 0.27	12.41	< 0.001
CpG6	6.04 ± 2.78	14.43 ± 1.65	39.81	< 0.001	3.20 ± 0.46	8.37 ± 1.34	44.36	< 0.001
CpG7	9.54 ± 6.92	14.71 ± 2.33	10.56	< 0.001	2.09 ± 0.31	15.64 ± 2.01	80.37	< 0.001
CpG8	10.89 ± 1.04	11.01 ± 1.02	1.32	0.187	10.92 ± 0.69	10.86 ± 1.26	0.51	0.608
CpG9	6.79 ± 4.98	28.49 ± 4.26	52.36	< 0.001	1.37 ± 0.35	11.23 ± 1.02	111.10	< 0.001
CpG10	10.13 ± 0.96	10.25 ± 0.88	1.59	0.113	10.01 ± 0.83	10.21 ± 1.04	1.88	0.061
CpG11	55.98 ± 4.39	56.17 ± 2.54	0.57	0.567	55.62 ± 3.87	58.28 ± 4.77	1.34	0.180
CpG12	5.19 ± 0.90	12.31 ± 1.70	63.09	< 0.001	5.12 ± 0.69	5.44 ± 1.04	1.19	0.235
CpG13	3.18 ± 0.71	9.66 ± 2.58	42.73	< 0.001	3.13 ± 0.68	4.57 ± 1.24	1.13	0.261
CpG14	6.22 ± 2.08	10.26 ± 0.43	28.07	< 0.001	4.25 ± 0.77	7.83 ± 1.26	29.93	< 0.001
CpG15	4.17 ± 1.91	6.24 ± 1.55	13.24	< 0.001	2.11 ± 0.27	5.85 ± 0.54	1184.00	< 0.001
CpG16	7.10 ± 1.72	14.53 ± 3.82	30.58	< 0.001	7.76 ± 1.02	8.04 ± 2.13	1.45	0.148
CpG17	3.10 ± 2.04	12.46 ± 3.18	52.62	< 0.001	1.06 ± 0.27	4.78 ± 1.11	39.40	< 0.001
CpG18	1.44 ± 0.84	3.27 ± 0.48	28.94	< 0.001	0.56 ± 0.12	2.16 ± 0.33	55.44	< 0.001

Note: PTSD, posttraumatic stress disorder; CpG, cytosine-guanine dinucleotide; SD, standard deviation. The measurement data was presented as mean ± standard deviation. Enumeration data are expressed as percentage or frequency and analyzed by *Chi*-square test. Comparisons between two groups were analyzed using *t*-tests.

CpG10, and CpG11 in the BDNF promoter were found between the control and PTSD groups ($p > 0.05$); differences in the methylation levels at CpG1, CpG2, CpG3, CpG4, CpG5, CpG6, CpG7, CpG9, CpG12, CpG13, CpG15, CpG16, CpG17, and CpG18 of BDNF promoter between the control and PTSD groups were statistically significant ($p < 0.05$) (**Table 2**).

Significant differences in the methylation levels of CpG1, CpG2, CpG3, CpG4, CpG5, CpG6, CpG7, CpG9, CpG14, CpG15, CpG17, and CpG18 in the promoter groups ($p < 0.001$). These results suggested that the methylation of CpG in BDNF gene promoter was closely related to PTSD, and the methylation level of CpG in the BDNF gene promoter may serve as a biomarker for PTSD diagnosis.

Types of trauma in PTSD patients may affect the methylation level of BDNF gene promoter

Next, the correlation between the methylation level of CpG1-18 in BDNF gene promoter and the types of trauma of PTSD patients was analyzed. The results (**Table 3**) revealed that the methylation levels of CpG1 and CpG18 were significantly associated with aggressive violent trauma, methylation level of CpG7 was correlated to traffic accident trauma, while the methylation level of at the other loci in the CpG island was not related to the types of trauma of PTSD patients though after multiple correction. These results indicate that the types of trauma of PTSD patients may have a certain effect on the methylation level of BDNF gene promoter.

Single-factor regression analysis for factors influencing PTSD

Whether the patient underwent PTSD served as an independent variable and methylation level of BDNF promoter, depressive degree score, poor sleep quality score, early trauma score, mental stress score, and trauma type as dependent variables, a single-factor regression analysis was conducted. Results (**Table 4**) showed that the methylation level of the BDNF promoter, depressive degree score, poor sleep quality score, early trauma score, mental stress score, and trauma type were closely related to the occurrence and development of PTSD (all $p < 0.05$).

Table 3. Correlation analysis between the types of trauma and methylation level of BDNF of PTSD patients

Type of Trauma	CpG1	CpG2	CpG3	CpG4	CpG5	CpG6	CpG7	CpG8	CpG9	CpG10	CpG11	CpG12	CpG13	CpG14	CpG15	CpG16	CpG17	CpG18
Sexual assault																		
Spearman's *r*	0.015	0.021	0.111	0.024	0.065	0.031	0.026	0.034	0.026	-0.042	-0.044	0.040	0.046	-0.038	0.029	0.034	0.029	0.019
p value	0.793	0.702	0.050	0.664	0.242	0.584	0.648	0.545	0.645	0.456	0.434	0.477	0.412	0.499	0.604	0.542	0.600	0.732
Assaultive violence																		
Spearman's *r*	0.166	0.003	0.078	0.041	0.095	0.017	0.022	0.016	0.018	0.027	0.032	0.023	0.038	0.005	0.015	0.009	0.021	0.175
p value	0.003	0.953	0.165	0.459	0.089	0.755	0.695	0.771	0.742	0.626	0.570	0.685	0.493	0.922	0.786	0.872	0.711	0.002
Traffic accident																		
Spearman's *r*	0.176	0.010	-0.060	0.072	0.028	0.280	0.273	0.110	-0.271	0.134	0.140	0.136	0.138	-0.288	0.038	-0.045	-0.045	0.038
p value	0.002	0.855	0.284	0.199	0.614	< 0.001	< 0.001	0.050	< 0.001	0.010	0.012	0.014	0.064	0.086	0.159	0.362	0.137	0.245
Death of a Close One																		
Spearman's *ρ*	0.046	0.026	-0.039	0.038	0.036	0.021	0.031	0.044	-0.029	0.054	0.054	0.047	0.060	-0.006	0.024	-0.035	-0.045	0.043
p value	0.408	0.647	0.483	0.499	0.525	0.701	0.581	0.435	0.599	0.330	0.330	0.399	0.285	0.920	0.662	0.532	0.679	0.446
Spearman's *ρ*	0.010	0.019	-0.026	0.073	0.018	0.081	0.075	0.054	-0.072	0.059	0.055	0.057	0.052	-0.082	0.075	-0.062	-0.083	0.014
p value	0.855	0.733	0.639	0.194	0.749	0.147	0.179	0.334	0.198	0.295	0.327	0.304	0.354	0.140	0.182	0.268	0.138	0.797

Note: According to CAPS and DSM IV, the correlation between the type of trauma and the methylation of BDNF promoter was scored, the type of trauma was classified by the total trauma events experienced by patients, and the Spearman correlation coefficient and related *p* value and corrected *p* value of each trauma type were analyzed.

Table 4. Regression analysis of influence factors for PTSD

Variants	B	SE	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
PTSD Severity (Clinician-rated)	0.062	0.009	45.773	1	< 0.001	1.064	1.045	1.083
PTSD Severity (Self-reported)	0.107	0.014	60.330	1	< 0.001	1.113	1.083	1.143
Depression Severity	0.224	0.029	71.429	1	< 0.001	1.277	1.207	1.351
Poor Sleep Quality	0.275	0.039	49.917	1	< 0.001	1.316	1.219	1.420
Early Trauma Exposure	0.748	0.093	65.373	1	< 0.001	2.113	1.763	2.534
Psychiatric Distress	2.510	0.290	75.111	1	< 0.001	12.304	6.795	21.704
CpG1	-6.822	1.270	28.856	1	< 0.001	0.000	0.000	0.013
CpG2	-0.160	0.076	4.365	1	0.037	0.852	0.734	0.990
CpG3	0.161	0.081	3.969	1	0.046	1.174	1.003	1.376
CpG4	0.297	0.142	4.337	1	0.036	1.346	1.019	1.778
CpG5	-0.663	0.323	4.202	1	0.040	0.515	0.274	0.971
CpG6	-0.087	0.041	4.545	1	0.035	0.917	0.846	0.994
CpG7	-0.035	0.017	4.428	1	0.035	0.966	0.935	0.998
CpG9	0.047	0.023	4.201	1	0.040	1.048	1.002	1.096
CpG14	0.088	0.044	3.958	1	0.047	1.092	1.001	1.192
CpG15	0.130	0.061	4.518	1	0.034	1.139	1.010	1.284
CpG17	0.119	0.056	4.477	1	0.034	1.126	1.009	1.258
CpG18	-0.218	0.099	4.903	1	0.027	0.804	0.662	0.975

Note: PTSD, posttraumatic stress disorder; CpG, cytosine-guanine dinucleotide; SD, standard deviation; CI, confidence interval.

Discussion

BDNF in neurobiological mechanisms in stress and memory disorders has been widely noticed in extensive clinical and preclinical studies [15, 16]. With rapid development of epigenetics and DNA methylation detection technology, it is possible for us to study the pathogenesis of PTSD and search for gene therapy from the perspective of DNA methylation [17, 18]. In the present study, we explored methylation of BDNF gene and different loci on the occurrence and development of PTSD, and found that methylation level of CpG in BDNF promoter may be a biomarker for diagnosing PTSD.

BDNF plays a pleiotropic role in the development of the central nervous system and synaptic plasticity that underlie cognitive function and circuit formation [19]. A recent study has shown that epigenetic mechanisms, like modification of DNA in the form of DNA (cytosine-5) methylation, have critical effects on the activity-dependent regulation of BDNF and other genes [20]. In addition, methylation of cytosine residues in most cases is stable in chemistry and biology over time and epigenetic changes may be reversed by treating with pharmacological drugs or environmental stimuli, while gene changes are irreversible [21]. Therefore, much attention has been focused on the relationship between the hypermethylation of promoter-associated CpG islands and transcriptional activity of genes and the application of DNA methylation patterns being a biomarker in human cancer and multifactorial or complex disorders [22]. Certain evidence has demonstrated that BDNF regulation of the expression of dopamine D3 receptor (DRD3) is implicated in drug addiction, schizophrenia and Parkinson's disease [23, 24]. Moreover, tabulations based on the DNA methylation spectrum of the BDNF gene CpG island may be a critical diagnostic biomarker for major depression [25]. In addition, hypermethylation of the BDNF promoter is associated with an increase in the risk of suicide and neuroblastoma pathogenesis in healthy people [26, 27]. Hypermethylation of the BDNF promoter has been demonstrated leading to hippocampal dysfunction due to cognitive diseases and traumatic stress, which are remarkable characteristics of PTSD's physiological path [28].

Our results show that methylation of CpG in BDNF gene promoter is closely related to PTSD,

and that methylation level of CpG in BDNF gene promoter may serve as a biomarker for PTSD diagnosis. Current evidence shows that serum BDNF levels are decreased in acute mania, depression euthymic bipolar disorder (BD), and bipolar depression, and are lower with longer course of diseases [29]. The levels of serum/plasma BDNF in manic and depressive episodes continue to decrease and then return to normal levels in acute manic patients [30]. A comprehensive study exhibited that in frontal cortex, there are evidences of psychosis related DNA methylation differences in numerous loci, such as various involved in brain development, glutamatergic and GABAergic neurotransmission, and other processes associated with the etiology of disease [31]. Another study demonstrated elevated methylation of BDNF promoter 1 in frontal cortex tissue of BD brains [32]. Furthermore, the level of methylation of BDNF gene promoter in BD II and major depressive disorder (MDD) patients was higher than that in BD I group, and when the emotional state is stratified, the level of methylation in patients with depression was significantly higher, in comparison to the levels of manic/mixed patients [33]. Moreover, recent research results suggested that changes in methylation of BdnfDNA in hippocampus may contribute to the continuous impairment of hippocampal functioning that can persist for many years after emotional trauma in PTSD patients [34, 35]. Therefore, the basis of such long-term adverse effects of emotional trauma on new memory processing in people may be associated with methylation changes of hippocampus-specific DNA of the Bdnf gene [15]. DNA methyltransferase blockers cause low methylation and improve depressive behavior [36]. These findings suggest that methylation abnormalities in BDNF promoter region may be involved in the pathogenesis of depression. Methylation status may be a biomarker for the diagnosis and prognosis of depression, and provide a new direction for the research and development of antidepressants.

Altogether, our study demonstrates that methylation of the BDNF gene promoter acts as a potent diagnostic biomarker in post-traumatic stress disorder, providing a potential new basis for treatment and diagnosis for PTSD. However, there is still controversy over the effects of methylation of BDNF gene on PTSD, due to the lack of related technologies, restrictions and the complexity of the metabolic process. Further study of working mechanism of methylation of BDNF gene still needed to provide better treatment therapy for PTSD. PTSD is thus attracting more and more attention from society. With the application of biochemistry, genetics, and human genome engineering in the study of PTSD etiology, it is sure that there will be new breakthroughs in its pathogenesis research and provide new research directions.

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Disclosure of conflict of interest

None.

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