

## Original Article

## Traumatic life events in bipolar disorder: impact on BDNF levels and psychopathology

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**Background:** There is evidence that vulnerability to depression and anxiety disorders is markedly increased by traumatic life events. While childhood abuse has been reported to be associated with poorer outcomes in bipolar disorder, little is known about the neurobiological basis underlying this association. The aim of this study was to ascertain whether bipolar patients who were exposed to a traumatic event or events (TE) have lower brain-derived neurotrophic factor (BDNF) levels and more severe psychopathology as indicated by increased comorbidity and other clinical features when compared to those who were not exposed to TE.

**Methods:** One-hundred and sixty-three consecutively recruited bipolar outpatients were assessed by Structured Clinical Interview for DSM-IV (SCID) and standard protocol in order to evaluate psychopathology and clinical features. The reported TE was assessed using DSM-IV stem criteria for trauma (as defined by A1 and A2 criteria for trauma for post-traumatic stress disorder). Subjects were divided into 2 groups according to presence or absence of lifetime TE. The levels of BDNF, comorbidity and other clinical features were compared between groups.

**Results:** After adjusting for confounders, results indicated that bipolar patients with a history of TE have alcohol abuse/dependence ( $p < 0.001$ ), anxiety comorbidity, and lower levels of serum BDNF ( $p < 0.01$ ) compared to those without a history of TE. There was no difference between the 2 groups in age of onset, presence of psychosis, other substance abuse and dependence, rapid cycling or suicide attempts.

**Conclusions:** Our findings suggest that TE are associated with significantly increased prevalence of alcohol and anxiety comorbidity as well as lower BDNF levels in bipolar patients. It is possible that a decrease in BDNF levels may account for increased comorbidity, but further prospective studies are required to confirm this.

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There is strong evidence that vulnerability to depression and anxiety disorders is markedly increased by childhood abuse, including physical and sexual, as well as adulthood stressors. Epidemiological studies and clinical trials with large

samples have revealed that stress and emotional trauma are associated with increased risk of psychopathology (1) and attempted suicide (2), particularly when experienced early in life (2, 3). The impact of a traumatic event or events (TE) on mental health is not fully explained by genetic predisposition. For instance, a study of female twins showed that stressful life events are significant predictors of the onset of major depression even in the absence of a high genetic risk (4). In

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addition, the association between childhood abuse or traumatic life events and the development of post-traumatic stress disorder (PTSD) is well known. Furthermore, research data has shown a significant relationship between childhood trauma and other psychiatric disorders in later life including panic disorder (5), any anxiety disorder in children (6), eating disorders (7), obsessive-compulsive disorder (OCD) (8), substance abuse (1) and multiple personality disorder (9). Childhood maltreatment strongly predicts poor psychiatric and physical health outcomes in adulthood in that these individuals are more likely to become high utilizers of medical care and emergency services (10).

In comparison to the extensive literature regarding the links between adverse life events and depression, few studies have examined the association between TE and their impact on bipolar disorder (BD). These studies report that TE are highly prevalent among bipolar individuals and are associated with the triggering of bipolar episodes and also with poorer outcomes (11–13). Leverich et al. (14) examined the impact of childhood trauma on the course of bipolar illness and found that a history of physical or sexual abuse was associated with earlier onset of illness, increased comorbidity and higher rates of suicide attempts. A recent study (12) found a history of childhood abuse in half of the patients with BD and, in this sample, childhood abuse was associated with lifetime substance misuse comorbidity, rapid cycling and suicide attempts. Post-traumatic stress disorder comorbidity is also prevalent with rates of PTSD ranging from 7–19% for outpatient bipolar samples (15–17). One-third of bipolar patients with a history of childhood abuse manifest comorbid adult PTSD (13) and bipolar patients with comorbid PTSD are more likely to present multiple Axis I disorders, low social support and greater trauma exposure (17).

Notwithstanding the reported association between TE and an adverse course of BD, little is known regarding neurobiological mediators of this interaction. Brain-derived neurotrophic factor (BDNF) may be a potential candidate. Alterations in BDNF levels and genes have been implicated in both mood disorders and stress (18). BDNF plays a diverse role in regulating neuronal survival, structure, and function including playing a critical role in the development and function of central serotonin neurons. Decreased BDNF levels have been reported among depressed patients (19). Three independent studies reported that serum BDNF levels were reduced in unipolar depressed patients and were negatively correlated with the

severity of depressive symptoms (20). There are recent data suggesting the involvement of BDNF in the pathophysiology of BD. For instance, serum BDNF levels were found to be negatively correlated with the severity of manic and depressive symptoms (21). In an animal model of mania, amphetamine decreased, while lithium and valproate increased, BDNF levels (22). Family-based association studies also have reported that polymorphisms in the BDNF gene may be involved in BD (23, 24).

Intriguingly, to date, there is no data regarding BDNF levels in patients with PTSD, or in those with a history of childhood abuse. However, smaller hippocampal volumes in patients with early life stress, child sexual abuse (25), PTSD (26, 27) and depression have been reported in comparison to normal controls (28). It is conceivable that TE may lead to adverse clinical outcome through a reduction in BDNF levels with a consequent reduction in hippocampal volumes. BDNF val66met polymorphism has been found to be associated with decreased hippocampal volume in humans (29). Depressed women with a history of child abuse have an 18% smaller mean left hippocampal volume than non-abused women (30). Remarkably, these apparent differences in hippocampal size may be reversible with antidepressant treatment, consistent with a function of neurotrophic factors in both neural plasticity and neurotrophism within the hippocampus (18). Additionally, animal models of chronic and acute stress have demonstrated increased cortisol levels and decreased BDNF levels in the hippocampus (31). Taken together, these data suggest that BDNF might be a neurobiological substrate that mediates the environmental effects on the psychopathology.

The aim of the present study, therefore, was to evaluate whether bipolar patients with a history of TE have lower BDNF levels and more severe psychopathology as indicated by increased comorbidity and other clinical features. Second, we aimed to investigate whether the BDNF levels are affected by a history of trauma independent of development of PTSD diagnosis.

### Methods

One hundred and sixty-three bipolar outpatients were consecutively recruited from the Bipolar Disorders Program of the University Hospital at the Federal University, Porto Alegre, Brazil, between September 2003 and August 2005. The subjects were assessed by Structured Clinical Interview for DSM-IV (32) – Axis I (SCID-I) for diagnosis and a standard protocol in order to

evaluate psychopathology and clinical features. Patients with BD type I and type II were included and all patients gave written informed consent before entering the study. The present study was approved by the local ethical committee. The presence of substance abuse/dependence, anxiety comorbidity, rapid cycling and lifetime psychosis was determined using DSM-IV criteria (32). Anxiety comorbidity group included panic disorder with or without agoraphobia, agoraphobia without panic disorder, OCD, generalized anxiety disorder, social phobia, specific phobia, PTSD, and anxiety disorder not otherwise specified. Global functioning was assessed using the Global Assessment of Functioning Scale. Depressive and manic symptoms were assessed using the Hamilton Depression Rating Scale-17 items (HDRS), and Young Mania Rating Scale (YMRS), respectively.

The sample ( $n = 163$ ) was divided into 2 major groups: patients with- ( $n = 78$ ) and without-lifetime exposure ( $n = 85$ ) to a TE. The reported TE was assessed using DSM-IV A1 and A2 criteria. The DSM-IV definition of trauma, as used for the diagnosis of PTSD, includes objective (A1 – exposure to traumatic event) and subjective (A2 – presence of fear or helplessness) components. Criteria A1 and A2 from the PTSD module of the SCID were the basis used to determine lifetime traumatic exposure since many patients did not exhibit PTSD comorbidity and the other symptoms for a diagnosis were not present. The reported trauma was grouped into 4 major categories (12, 14): sexual abuse, physical abuse, psychological abuse, and ‘other traumatic events’. ‘Other traumatic events’ included loss of a close relative, car accident, or a personal accident.

Five mL of blood were withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube. The blood was immediately centrifuged at 3000  $g$  for 5 min, and serum was kept frozen at  $-80^{\circ}\text{C}$  until assayed. BDNF serum levels were measured with sandwich-enzyme-linked immunosorbent assay, using a commercial kit according to the manufacturer’s instructions (Chemicon, Temecula, CA). Briefly, microtiter plates (96-well flat-bottom) were coated for 24 h with the samples diluted 1:2 in sample diluents and the standard curve ranged from 7.8–500 pg of BDNF. Plates were then washed 4 times with wash buffer, monoclonal anti-BDNF rabbit antibody was added (diluted 1:1000 with sample diluents) and incubated for 3 h at room temperature. After washing, a second incubation with peroxidase conjugated anti-rabbit antibody (diluted 1:1000) for 1 h at room temperature was carried out. After the addition of streptavidin-enzyme, substrate and

Table 1. Demographics

Variable	Bipolar patients		p
	Absence of trauma ( $n = 85$ )	Presence of trauma ( $n = 78$ )	
Sex			0.370 <sup>a</sup>
Men	31.1%	25.0%	
Women	68.9%	75.0%	
Age (years)			
Mean (SD)	43.01 (11.21)	42.13 (12.00)	0.616 <sup>b</sup>
<40	35.6%	44.0%	0.413 <sup>a</sup>
40–59	61.1%	51.2%	
$\geq 60$	3.3%	4.8%	
Schooling (years)			
Mean (SD)	9.86 (4.19)	9.09 (4.27)	0.243 <sup>b</sup>
0–8	36.0%	39.5%	0.187 <sup>a</sup>
9–11	34.9%	43.2%	
$\geq 12$	29.1%	17.3%	

<sup>a</sup>Chi-square test; <sup>b</sup> $t$ -test.

stop solution, the amount of BDNF was determined (absorbance set in 450 nm). The standard curve demonstrates a direct relationship between optical density and BDNF concentration. Total protein was measured by Lowry’s method using bovine serum albumin as a standard.

#### Statistical analysis

Clinical features and comorbidity were compared between the 2 groups, (i.e., presence or absence of TE), using  $\chi^2$ -tests or  $t$ -tests as indicated in Tables 1 and 2. The BDNF levels were compared between groups using a one-way analysis of variance (ANOVA) test for heterogeneity. The individual differences were assessed using a *post-hoc* Dunnett test if the ANOVA was significant. A linear regression model was used in order to control for confounders;  $p < 0.05$  was considered statistically significant.

#### Results

The socio-demographic characteristics of BD patients are summarized in Table 1. BD patients with ( $n = 78$ ; 47.8%) and without ( $n = 85$ ; 52.1%) a history of TE did not differ in terms of gender, age or years of schooling. The ethnicity was assessed as white ( $n = 135$ ) or non-white ( $n = 25$ ) and the distribution of ethnicity was not different between patients with trauma and without trauma ( $p = 0.079$ ).

The prevalence of PTSD in this sample was 16.5%. Among the 163 bipolar patients, 59.1% were taking lithium, 32.9% valproate, 8.1% carbamazepine and 1.8% lamotrigine; 42.3% were

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Table 2. Clinical features

Variable	Bipolar patients		p
	Absence of trauma (n = 85)	Presence of trauma (n = 78)	
Age of onset	25.02 (11.7)	25.55 (12.91)	0.771 <sup>a</sup>
Number of suicide attempts	1.63 (2.25)	2.16 (1.86)	0.172 <sup>a</sup>
Rapid cycling			0.992 <sup>b</sup>
Presence	26.4%	26.5%	
Absence	73.6%	73.5%	
Psychosis			0.739 <sup>b</sup>
Presence	44.4%	49.0%	
Absence	55.6%	51.0%	
Alcohol abuse			0.001 <sup>b</sup>
Presence	21.1%	31.0%	
Absence	78.9%	69.0%	
Alcohol dependence			0.001 <sup>b</sup>
Presence	7.8%	26.2%	
Absence	92.2%	73.8%	
Drug abuse			0.658 <sup>b</sup>
Presence	75.6%	72.6%	
Absence	24.4%	27.4%	
Drug dependence			0.665 <sup>b</sup>
Presence	83.3%	85.7%	
Absence	16.7%	14.3%	
Anxiety disorder			0.001 <sup>b</sup>
Presence	45.6%	82.1%	
Absence	54.4%	17.9%	
GAF	63.42 (15.62)	61.83 (12.69)	0.464 <sup>a</sup>
HDRS	8.71 (6.57)	11.20 (7.96)	0.025 <sup>a</sup>
YMRS	4.80 (5.95)	4.26 (4.97)	0.531 <sup>a</sup>

GAF = Global Assessment of Functioning; HDRS = Hamilton Depression Rating Scale-17 items; YMRS = Young Mania Rating Scale.

<sup>a</sup>t-test; <sup>b</sup>chi-square test.

taking antipsychotics and 15.3% were taking antidepressants. There was no significant difference between patients with- and without-trauma regarding antidepressant use (11.5% versus 18.8%;  $\chi^2 = 4.04$ ,  $df = 5$ ,  $p = 0.671$ ) and antipsychotic use (42.3% versus 41.1%;  $\chi^2 = 3.7$ ,  $df = 4$ ,  $p = 0.439$ ). More patients were on lithium (65.9% versus 41.0%) and fewer on valproate (22.4% versus 38.5%) ( $\chi^2 = 7.94$ ;  $df = 2$ ;  $p = 0.019$ ) among those without a history of trauma compared to those with trauma. Rates of carbamazepine and lamotrigine usage did not differ between groups.

Clinical characteristics of the sample are shown in Table 2. After adjusting for confounders, which included gender, age, schooling years and HDRS scores, the bipolar patients with a history of TE were more likely to have alcohol abuse ( $p < 0.001$ ), alcohol dependence ( $p < 0.001$ ) and anxiety comorbidity ( $p < 0.001$ ). As expected, a history of TE was highly correlated with PTSD

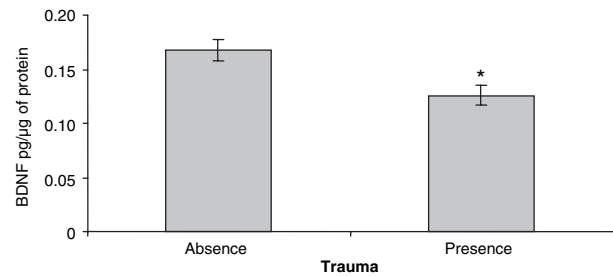


Fig. 1. Brain-derived neurotrophic factor (BDNF) levels in presence or absence of trauma in bipolar patients. \*Analysis of variance ( $p = 0.002$ ).

comorbidity ( $p < 0.01$ ). However, PTSD was not associated with alcohol abuse ( $p = 0.654$ ) or dependence ( $p = 0.523$ ). Patients with a history of TE had higher scores on the HDRS ( $p < 0.025$ ), but there was no difference between groups on the YMRS scores, presence of psychosis, age at onset of illness, other substance abuse and dependence, rapid cycling or suicide attempts. Furthermore, the number of previous depressive or manic episodes did not differ ( $p > 0.05$ ) between subjects exposed to TE (depressive episodes, mean = 9.0, manic episodes, mean = 7.8) and those not exposed to TE (depressive episodes, mean = 8.1, manic episodes, mean = 7.3).

BDNF was found to be decreased in bipolar patients with a history of trauma ( $p = 0.002$ ) (Fig. 1). In a regression model controlled for sex, age, and mood symptoms (as measured by YMRS and HDRS), trauma was significantly related to lower BDNF levels ( $\beta = -0.265$ ; confidence interval =  $-0.072$  to  $-0.019$ ;  $p = 0.001$ ). No correlation was found between HDRS scores and BDNF levels ( $r = 0.007$ ;  $p = 0.928$ ). Additionally, no difference in BDNF levels was found in patients with or without comorbid PTSD (ANOVA,  $F = 0.842$ ;  $p = 0.360$ ), alcohol abuse ( $p = 0.123$ ) or alcohol dependence ( $p = 0.989$ ), rapid cycling ( $p = 0.704$ ), or history of suicide attempts ( $p = 0.527$ ). The prevalence of the subtypes of TE was 12.6% for sexual abuse, 6.9% for physical abuse, 6% for psychological abuse and 31.7% for 'other TE' (Fig. 2). 'Other TE' includes loss of a close relative (10.3%), car accident (5.1%), personal accident, or witnessing a life threatening situation of someone else (16.3%). More than one type of trauma was reported by 9.4% of subjects and for statistical analytical purposes, these subjects were included in both categories of subtypes of TE. The cumulative effect of trauma was not examined in the present study. The type of trauma was considered as an independent variable in relation to BDNF levels. Among the different kinds of traumatic events, sexual abuse had the strongest effect

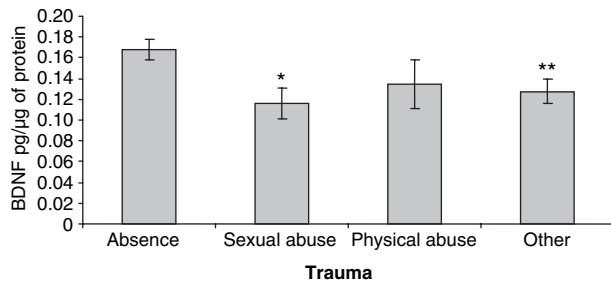


Fig. 2. Brain-derived neurotrophic factor (BDNF) levels in absence or presence of different types of trauma in bipolar patients. \*Sexual abuse versus absence of trauma, *post-hoc* Dunnett test ( $p = 0.02$ ). \*\*Other types of trauma versus absence of trauma, *post-hoc* Dunnett test ( $p = 0.014$ ).

on BDNF levels in an analysis of covariance. Of the 22 patients who reported sexual trauma, 18 were women and 4 were men. However, gender had no effect on the BDNF levels ( $p = 0.932$ ).

## Discussion

Our results suggest that presence of lifetime TE is highly prevalent among bipolar individuals. Furthermore, those with a history of TE are more likely to have alcohol abuse/dependence and anxiety comorbidity, PTSD, as well as more severe depressive symptoms. However, PTSD was not associated with alcohol abuse ( $p = 0.654$ ) or dependence ( $p = 0.523$ ). This suggests that lifetime TE has an impact on the course of BD independent of a PTSD diagnosis. These data are in agreement with previous reports indicating an increased incidence of comorbid disorders, including alcohol abuse/dependence, in bipolar patients with-trauma exposure (12, 14). While previous studies have reported increased suicide attempts, drug abuse, early age at onset and rapid cycling in the bipolar patients who experienced childhood abuse, we did not find such associations in this sample. The reasons for this discrepancy may be related to characteristics of the sample and methods of data assessment. First, the TE was considered according to DSM-IV criteria, which could include both childhood and adulthood traumatic events since the time of the event was not assessed. The 2 major studies referred above assessed only childhood abuse. Second, our sample was comprised of outpatient bipolar subjects from an academic specialty centre, and our sample size was smaller than a previous study, which examined child abuse in BD (14).

In addition to a more severe clinical presentation, bipolar patients with a history of trauma also had decreased serum BDNF levels. To our knowledge, this is the first study to assess serum BDNF

levels in bipolar patients exposed to traumatic life events. The findings of this study support our hypothesis that BDNF levels are decreased in bipolar patients with a history of trauma. In a recent previous study we showed that during the acute phases of the disorder (mania and depression), bipolar patients have lower levels of BDNF (21) whereas euthymic patients have BDNF levels at the same range as healthy control subjects. In the present study, traumatic events remained associated with lower BDNF levels even after controlling for manic and depressive symptoms. Furthermore, no correlation between HDRS scores and BDNF levels ( $r = 0.007$ ;  $p = 0.928$ ) was found in this sample. These data suggest that the exposure to TE has an effect independent of mood status on BDNF levels. The differences in BDNF levels were not explained better by other factors such as alcohol abuse or dependence, rapid cycling, suicide attempts or PTSD comorbidity as the exposure to traumatic events seems to have an independent effect on BDNF levels.

Among traumatic events, sexual abuse showed the strongest association with a reduction in BDNF levels. Consistent with previous reports, the sexual trauma was more prevalent among females in our sample. However, the gender had no effect on the BDNF levels. Previous clinical studies addressing differences across abuse subtypes found suicidality was associated with sexual but not with emotional or physical trauma (12). In another study, comorbid adult PTSD was associated in particular with a history of sexual abuse (13). Childhood sexual abuse also has been repeatedly associated, in adulthood, with depression with physical complaints (10). In this context, our results provide additional evidence suggesting that a sexual component makes the greatest impact on psychopathology and BDNF levels.

Significant limitations dictate that the results should be interpreted with caution. First, the reliability of bipolar patients' reports of past traumatic events may vary, given the possible association with recall bias and poor insight. Self-reported trauma requires caution when interpreting the results, although Goodman et al. (33) observed good reliability in the longitudinal assessment of trauma histories among psychiatrically ill women. The possible bias involved is usually under-reporting, particularly regarding early abuse (34). Second, the temporal and cumulative possible effects of trauma were not assessed nor considered in the analysis. The presence of a traumatic event was considered as a dichotomous variable (i.e., lifetime presence or absence). In this context, only the association can be inferred from data, but no

causative evidence can be assumed. Third, it cannot be ruled out that the use of medication may have altered the levels of BDNF, since it is well established that psychotropic medications may change BDNF levels. However, it is unlikely that medication would account for the correlation between the levels of BDNF and TE exposure. There was no significant difference between patients with- and without-trauma regarding antidepressant use and antipsychotic use. Patients who did not present a history of trauma presented higher rates of use of lithium, but also a diminished rate of use of valproate in comparison to those with a history of trauma. It has been demonstrated that lithium and valproate increase BDNF levels (22). Rates for the use of carbamazepine and lamotrigine did not differ between groups. Finally, the BDNF was measured in serum. There may be other sources for serum BDNF, although at present they have not been identified. However, it has been demonstrated that BDNF can cross the blood-brain barrier, and there is a high positive correlation ( $r = 0.81$ ) between serum and cortical BDNF levels (35). Therefore, it has been suggested that the changes of plasma BDNF levels may partly reflect the changes of brain BDNF secretion (36).

It must be acknowledged that the BDNF is complex and influenced by a number of factors. BDNF has been implicated in the pathogenesis of mood disorders and in the mechanism of action of therapeutic agents such as mood stabilizers and antidepressants (18). In preclinical studies, BDNF expression has been shown to be regulated by stress responsive corticosteroids (37). Early life events may have long-term effects on adult health and well-being, in the form of repeated activation of stress responsive biological mediators such as glucocorticoids and catecholamines (38, 39). Notably, BDNF and other neurotrophic factors are believed to counteract the negative impact of stress hormones on hippocampal volume (40). Early exposure to traumatic life events and PTSD, as well as depression, has been associated with HPA axis dysfunction (41). A recent article from Schule et al. (42) showed that patients with BDNF gene met/met polymorphism had higher HPA axis activity during the dexametasone/corticotrophic-releasing hormone test.

The exposure to traumatic life events could partially explain the increased comorbidity by lowering BDNF levels, which could also account for the severity of symptoms, decreased hippocampus volume, and cognitive impairment (43). Conversely, the genetic predisposition to reduced levels of BDNF could contribute to higher vulnerability

to BD and the neurobiological effects of traumatic events. Other studies have investigated the relationship between polymorphisms of BDNF gene and vulnerability to BD. Some family-based association studies have shown that BDNF gene polymorphism val66met is associated with BD (44), but other studies could not confirm these results (45–47). No association was found in Japanese (45) and Chinese samples (46). One case-controlled study from the UK with 3,000 individuals did not find increased risk for BD in those with the polymorphism, but it was associated with rapid cycling (47). A recent study suggested that another polymorphic region designated as BDNF-linked complex polymorphic region, which affects transcriptional activity of BDNF, is associated with susceptibility to BD (48). Further studies, prospective and investigating polymorphisms of BDNF and PTSD or lifetime TE could help to clarify and extend these initial observations.

The data presented may open some clinical and research perspectives. A large clinical trial for depression showed that, among those with a history of early childhood trauma, psychotherapy alone was superior to antidepressant monotherapy and combination therapy was marginally superior to psychotherapy alone (49). The effect of childhood trauma was not as robust as it was thought to be, since its impact on final remission was not detected in relation to baseline scores in a recent erratum communication (49). However, there is no data regarding BDNF levels as an outcome of psychotherapy. A single study on panic disorder reported higher BDNF levels as a predictor of good response to cognitive behavior therapy (50). BDNF levels are also known to be increased by antidepressants (20). These data may help to match patients with an appropriate treatment in the future. We highlight the need for future studies regarding response to treatment in specific bipolar sub-groups of patients.

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