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Childhood Trauma Is Associated With Severe Clinical Characteristics of Bipolar Disorders

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ABSTRACT

Objective: Beyond genetic risk variants, the pathophysiology of bipolar disorders is likely to be partly determined by environmental susceptibility factors. Our study is one of the first to investigate, in a large sample of well-characterized bipolar patients, associations between clinical presentations and childhood trauma subtypes, including neglect and abuse items.

Method: 587 patients with *DSM-IV*–defined bipolar disorder were recruited from France and Norway between 1996–2008 and 2007–2012, respectively. History of childhood trauma was obtained using the Childhood Trauma Questionnaire. Clinical variables were assessed with the Structured Clinical Interview for *DSM-IV* Axis I Disorders (Norwegian sample) or the Diagnostic Interview for Genetic Studies (French sample).

Results: Earlier age at onset of bipolar illness, suicide attempts, rapid cycling, and an increased number of depressive episodes each had significant associations ($P \leq .001$) with at least 1 subtype of childhood trauma (emotional abuse, sexual abuse, and emotional neglect). Multivariate analyses investigating trauma variables together showed that both emotional and sexual abuse were independent predictors of lower age at onset ($P = .002$ for each) and history of suicide attempts (OR = 1.60 [95% CI, 1.07 to 2.39], $P = .023$; OR = 1.80 [95% CI, 1.14 to 2.86], $P = .012$, respectively), while sexual abuse was the strongest predictor of rapid cycling (OR = 2.04 [95% CI, 1.21 to 3.42], $P = .007$). Females reported overall higher childhood trauma frequency and greater associations to clinical expressions than males (P values $< .05$).

Conclusions: Our results demonstrate consistent associations between childhood trauma and more severe clinical characteristics in bipolar disorder. Further, they show the importance of including emotional abuse as well as the more frequently investigated sexual abuse when targeting clinical characteristics of bipolar disorder.

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Patients with psychiatric illnesses more frequently report a history of childhood trauma compared to the general population.[1–5] In bipolar disorders, there are indications that childhood trauma is associated with various clinical characteristics of severity, including an earlier onset of the illness,[6] a rapid-cycling course,[6] psychotic features,[7–10] a higher number of lifetime mood episodes,[11–13] and suicide ideation and attempts.[14] However, the quality of these studies has been reported to be relatively low,[15] thus reducing the level of evidence. A recent review of 18 association studies performed by Daruy-Filho and coworkers[15] highlighted several limitations: lack of use of a structured clinical interview for diagnosis, lack of use of a standardized trauma assessment, low sample size (fewer than 100 patients), and insufficient current mood state measures as a potential bias in trauma assessment. On the basis of the limitations above, only 1 study[14] fulfilled Fisher and Hosang's edited quality criteria.[16] Therefore, high-quality studies are required in order to further explore the relationship between childhood trauma and clinical severity of bipolar disorders.

Knowledge of how specific types of trauma are associated with clinical characteristics is still sparse. Childhood physical abuse and sexual abuse seem to be the strongest predictors of unfavorable clinical characteristics in bipolar disorders.[15,16] However, very few studies have focused attention on emotional abuse and neglect.[15] Interestingly, there is evidence of the specific implications of certain subtypes of trauma, particularly emotional abuse,[1,5] in patients with bipolar disorder. Indeed, higher prevalence of emotional abuse in patients with bipolar disorder compared to healthy controls has been reported, even after controlling for other types of abuse.[1,5] We have also suggested that, among trauma subtypes, emotional abuse could be the type most closely associated with an earlier age at bipolar illness onset.[5]

Finally, it has been postulated that females report childhood trauma more frequently than males.[17] Females also tend to be overrepresented in the diagnosis of bipolar disorder compared to males, although the exact gender distribution varies across studies.[18] Thus, investigating the relationship between gender, childhood trauma, and clinical characteristics of bipolar disorder would be of interest. Until now, this relationship has not been thoroughly investigated.

Our study is one of the first to investigate, in a large sample of bipolar disorder patients (N = 587), whether childhood trauma, including neglect (both emotional and physical) as well as abuse (emotional, physical, and sexual), is associated with a more severe clinical presentation (ie, lower age at onset, more suicide attempts, rapid cycling, mood episodes, and substance misuse). We also investigated whether there are dose effects of abuse on clinical characteristics. Second, we performed multilevel analyses to investigate whether specific subtypes of childhood trauma are driving associations

Clinical Points

- Childhood trauma, particularly emotional and sexual abuse, worsens the clinical expression of bipolar disorder.
- Bipolar patients exposed to childhood trauma have an earlier age at illness onset, increased prevalence of suicide attempts and rapid cycling, and greater proneness toward depression.
- Recognition of childhood trauma may help in the identification of patients with a more severe illness profile in order to personalize treatment strategies.

between childhood trauma and clinical characteristics. Last, the large sample provided us with sufficient statistical power to perform additional analyses to thoroughly investigate the effect of gender on these associations.

METHOD

Participants

Patients from France were included from 3 French university-affiliated psychiatry departments (in Paris/Créteil, Bordeaux, and Nancy). Patients from Norway were included as part of an ongoing study of severe psychiatric disorders (Thematically Organized Psychosis [TOP] Study) and recruited from psychiatric inpatient and outpatient units at 3 major hospitals in Oslo, Norway. For inclusion in the study, all patients had to have a diagnosis of bipolar disorder (type I, type II, or not otherwise specified [NOS]) according to *DSM-IV* criteria. The Norwegian project was approved by the Regional Committee for Medical Research Ethics and the Data Inspectorate. The local institutional review boards approved the French study. Written informed consent for participating in the study was obtained from all participants.

Clinical Assessment

In both countries, clinical assessment was carried out by trained psychiatrists, MDs or psychiatrists in training, and clinical psychologists. The French patients were interviewed with the French version of the Diagnostic Interview for Genetic Studies (DIGS),[19] which provides lifetime *DSM-IV* Axis I diagnoses. French patients were euthymic at inclusion (ie, Mania Rating Scale[20] and Montgomery-Asberg Depression Rating Scale[21] scores ≤ 5). Clinical variables collected with the DIGS included age at onset and lifetime history of rapid cycling and history of mixed episodes (both defined as in the *DSM-IV* criteria) during the course of the disorder. Several variables related to suicide attempts were also collected: lifetime history of suicide attempt and of violent suicide attempt (including hanging attempts, jumping from heights, and the use of knives or firearms), number of suicide attempts, and age at first suicide attempt. A similar approach was taken in the Norwegian sample using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I).[22] For both samples, age at onset was defined as the age at which the subject first met *DSM-IV* criteria for a major depressive, manic, hypomanic, or mixed episode. Duration of illness was calculated by current age at time of assessment minus age at onset.

Childhood Trauma Questionnaire

To measure childhood adverse events, we used the Childhood Trauma Questionnaire (CTQ), a retrospective questionnaire inquiring about traumatic experiences in childhood with 5 answers ranging from "never true" to "very often true," yielding a total score as well as 5 subscores: physical, emotional, and sexual abuse and physical and emotional neglect.[23] Reliability and validity of the CTQ have been demonstrated previously.[23] In this study, the short versions (28-item version) of the CTQ translated into Norwegian[24] or previously validated in French[25] were used. We used a score in the "moderate to severe" range as a cutoff to dichotomize each subscore and to classify subjects as having or not having a history of childhood trauma in that category, as recommended by Bernstein and Fink.[26] The French sample was euthymic at the time of CTQ assessment, while no standardized assessments were conducted in the Norwegian sample, apart from clinical judgment.

Statistical Analyses

All statistical analyses were performed with the packages PASW Statistics 18 (Release 18.0.1; SPSS Inc, Chicago, Illinois) and R (Version 2.12.0; Statistics Department, University of Auckland, Auckland, New Zealand). Continuous variables are presented as mean ± SD. As the continuous clinical variables (such as age at onset and number of episodes) were not normally distributed, nonparametric tests (Mann-Whitney or Kruskal-Wallis) were used to investigate clinical variables and childhood trauma, dichotomized into abuse and no abuse. For the simple linear regression analyses, the continuous clinical variables were log transformed. As the hypomanic/manic variable was still skewed after log transformation, it was excluded from the regression analysis. Reassuringly, although the childhood trauma subtypes significantly correlated with each other, the collinearity analyses for the regression analyses were found sufficient (variance inflation factor ≤ 1.4). As gender differences are suggested in both childhood trauma prevalence[17] and the effect of childhood trauma on pathology,[27] follow-up linear and logistic regression analyses were conducted stratified by gender. For the multiregression analyses, post hoc analyses were conducted controlling for gender and diagnosis (bipolar I, bipolar II, bipolar NOS). Because inclusion of diagnosis (bipolar I, bipolar II, bipolar NOS) did not improve the model, it was taken out of the final analyses. Duration of illness was also used as a covariate when investigating mood episodes, rapid cycling, and suicide attempts. For clinical characteristics for which prevalence differed between France and Norway (ie, duration of illness and rapid cycling), the recruitment site was added as a covariate in the model.

To avoid type I error, we corrected for number of childhood trauma variables tested (emotional neglect, physical neglect, physical abuse, sexual abuse, emotional abuse, and dose [number of types] of abuse) using a *P*

Table 1. Patient Demographic and Clinical Characteristics (N = 587)

Characteristic	Value
Age, mean ± SD, y	40.6 ± 13.6
Gender, n, male/female	234/353
Ethnicity, n (%)	
White	567 (96.6)
Other	20 (3.4)
Age at onset of bipolar disorder, mean ± SD, y	24.2 ± 10.1
Illness subtype, n (%)	
Bipolar I	425 (72.4)
Bipolar II	126 (21.5)
Bipolar NOS	36 (6.1)
Suicide attempts, n (%)[a]	211 (36.4)
Rapid cycling, n (%)[a]	114 (20.8)
No. of depressive episodes, mean ± SD	4.8 ± 5.5
No. of hypomanic or manic episodes, mean ± SD	4.6 ± 6.0
Psychotic episodes, n (%)[a,b]	247 (49.4)
Cannabis abuse, n (%)[a]	75 (12.9)
Alcohol dependence, n (%)[a]	53 (9.1)
Inpatient, n (%)[c]	49 (8.3)
Childhood trauma of moderate to severe intensity, n (%)	
Physical abuse[d]	55 (9.5)
Sexual abuse[e]	104 (18.0)
Emotional abuse[f]	156 (26.9)
Physical neglect[g]	73 (12.5)
Emotional neglect[h]	180 (31.3)
Any type of maltreatment	277 (49.6)
Two or more types of trauma	146 (26.2)

[a]Percentage based on the number of patients for whom data were available.
[b]Having at least 1 psychotic episode during the course of the illness.
[c]Hospitalized sometime during the last year (Norwegian sample) but, if so, not in the last 3 months (French sample).
[d]98.8% (n = 580) of the patients completed physical abuse subscale.
[e]99.0% (n = 581) completed sexual abuse subscale.
[f]98.8% (n = 580) completed emotional abuse subscale.
[g]98.8% (n = 580) completed emotional neglect subscale.
[h]98.3% (n = 577) completed physical neglect subscale.
Abbreviation: NOS = not otherwise specified.

value of .008 as a marker of significance. As the study was hypothesis-driven, with a priori ideas on directions, we decided that this *P* value was sufficient without the potential of losing important data.

RESULTS

Sociodemographics and Clinical Variables

Four hundred eighteen patients from France recruited between 1996–2008 and 169 patients from Norway recruited between 2007–2012 were included in this study. The total sample is presented in Table 1. Before the 2 samples were merged, comparison analyses were conducted between the 2 sites. Differences between samples were found concerning rapid cycling (France: 23% vs Norway: 16%) and alcohol dependence (Norway: 14% vs France: 7%); also, the French sample was older and thus had a longer illness duration than the Norwegian sample (see Supplementary eTable 1 at PSYCHIATRIST.COM). The difference between sites regarding rapid cycling did not persist after duration was considered as a confounding factor. The difference between sites regarding lifetime alcohol dependence remained significant ($P = .017$) even when age at interview was used as a covariate. The 2 samples were similar in terms of CTQ total score (France: 41.74 ± 12.88 vs Norway: 44.03 ± 16.43; $z = 0.88$, $P = .37$), and the frequencies of trauma subtypes were also similar, with the exception of physical neglect (more frequent in Norway; $P = .001$).

Because the effects of trauma on the clinical expression of bipolar disorder are not likely to be related to differences across sites, the samples were pooled and analyzed together. Analysis by gender showed that females overall reported a higher prevalence of childhood trauma than males (CTQ total score: females, 43.48 ± 14.83; males, 40.78 ± 12.54; $f = 3.60$, $t = -2.24$, $P = .025$).

Childhood Trauma and Clinical Characteristics

Associations between childhood trauma subtypes (dichotomized into presence and absence) and clinical characteristics of bipolar disorder are presented in Table 2. We found that age at onset of bipolar illness was lower in patients who had experienced various trauma subtypes, specifically, sexual abuse, emotional abuse, emotional neglect, and physical neglect. A significant dose relationship between childhood abuse and lower age at onset was also observed: patients exposed to more types of abuse had a significantly lower age at onset (Figure 1). Females with childhood sexual abuse reported earlier age at onset than females without childhood sexual abuse (20.09 ± 7.16 vs 24.27 ± 9.83 years, $r^2 = 0.04$, $P < .001$). Also, males with childhood sexual abuse reported earlier age at onset than males without childhood sexual abuse (21.68 ± 9.36 vs 26.21 ± 11.03 years, $r^2 = 0.02$, $P = .042$). Similar findings were observed for emotional abuse and emotional neglect (data not shown).

Suicide attempts (present/absent) were significantly associated with sexual and emotional abuse. A significant dose-dependent relationship between childhood abuse and suicide attempts was observed: patients exposed to more types of abuse (physical, sexual, and/or emotional abuse) significantly more frequently had a history of suicide attempts. Females with childhood sexual abuse were significantly more likely to report having made at least 1 suicide attempt than females without childhood sexual abuse (53.1% vs 38.2%, $r^2 = 0.02$, $P = .018$). Also, males with childhood sexual abuse were significantly more likely to report at least 1 suicide attempt than males without childhood sexual abuse (45.5% vs 26.7%); however, this remained at a trend level for statistical significance ($P = .07$). Similar findings were observed for emotional abuse (data not shown).

Rapid cycling was significantly associated with childhood trauma, specifically, sexual abuse and emotional abuse. Moreover, a significant dose relationship between childhood abuse and rapid cycling was observed: patients exposed to more abuse types (from 0 to 3 types of abuse; physical, sexual, and/or emotional) showed significantly increased prevalence of rapid cycling. Analysis according to gender demonstrated that females with sexual or emotional abuse presented a higher prevalence of rapid cycling than females without sexual or emotional abuse (sexual abuse: 34.2% vs 18.6%, $r^2 = 0.04$, $P = .005$; emotional abuse: 31.3% vs 18.4%,

Table 2. Childhood Trauma and Clinical Characteristics in Bipolar Disorder[a]

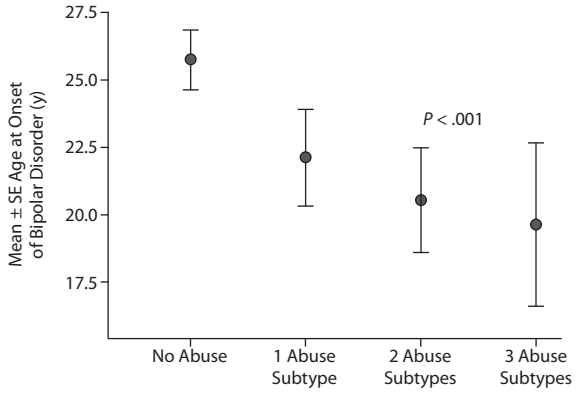
Characteristic	Emotional Neglect[b] Yes (n = 178) No (n = 389) Statistics	Physical Neglect[b] Yes (n = 71) No (n = 504) Statistics	Emotional Abuse[b] Yes (n = 153) No (n = 419) Statistics	Physical Abuse[b] Yes (n = 55) No (n = 517) Statistics	Sexual Abuse[b] Yes (n = 104) No (n = 467) Statistics	Abuse Dose Effect 3 Abuse Types (n = 22) 2 Abuse Types (n = 61) 1 Abuse Type (n = 114) None (n = 362) Statistics
Age at onset, mean ± SD, y[c]	22.63 ± 9.36 25.04 ± 10.44 U = 29,494.5, z = −2.84 **P = .005***	21.61 ± 10.06 24.60 ± 10.13 U = 13,798.5, z = −3.13 **P = .002***	21.20 ± 8.7 25.26 ± 10.36 U = 23,969.5, z = 4.63 **P < .001***	21.75 ± 8.15 24.47 ± 10.34 U = 12,067.5, z = −1.85 P = .065	20.42 ± 7.66 25.13 ± 10.42 U = 17,422.5, z = −4.51 **P < .001***	19.64 ± 7.05 20.54 ± 7.55 22.11 ± 9.49 25.74 ± 10.54 χ^2_3 = 29.2 **P < .001***[d]
Suicide attempts,[e] % yes/% no[b]	41.4/58.7 34.5/65.5 χ^2_1 = 2.44 P = .12	48.6/51.4 34.8/65.2 χ^2_1 = 5.19 **P = .02**	48.1/51.9 32.8/67.2 χ^2_1 = 11.28 **P = .001***	50.9/49.1 35.0/65.0 χ^2_1 = 5.42 **P = .02**	51.5/48.5 33.1/66.9 χ^2_1 = 12.69 **P < .001***	59.1/40.9 50.8/49.2 43.0/57.0 31.2/68.8 χ^2_3 = 16.57 **P = .001***[e]
Rapid cycling,[e] % yes/% no[b]	26.2/73.8 18.2/81.8 χ^2_1 = 4.52 **P = .03**	15.9/84.1 21.5/78.5 χ^2_1 = 1.12 P = .29	30.1/69.9 17.5/82.5 χ^2_1 = 10.35 **P = .001***	32.1/67.9 19.7/80.3 χ^2_1 = 4.42 **P = .04**	34.0/66.0 17.8/82.2 χ^2_1 = 12.27 **P < .001***	40.9/59.1 32.7/67.3 24.5/75.5 16.4/83.6 χ^2_3 = 15.04 **P = .002***[e]
No. of depressive episodes, mean ± SD[c]	5.41 ± 5.80 4.45 ± 5.28 U = 26,038.5, z = −2.41 **P = .016**	6.01 ± 6.50 4.61 ± 5.32 U = 14,206.0, z = −1.62 P = .10	6.30 ± 6.55 4.33 ± 5.05 U = 22,306.5, z = −3.42 **P = .001***	4.66 ± 5.30 4.81 ± 5.54 U = 11,875.5, z = −0.24 P = .81	5.48 ± 6.06 4.61 ± 5.34 U = 18,439.0, z = −1.63 P = .10	4.95 ± 5.40 5.73 ± 6.08 5.96 ± 6.51 4.25 ± 4.95 χ^2_3=8.72 **P = .03**[d]
No. of hypomanic or manic episodes, mean ± SD[c]	4.83 ± 6.12 4.54 ± 6.00 U = 30,296.0, z = −0.83 P = .41	4.90 ± 6.46 4.55 ± 5.94 U = 15,960.5, z = −0.61 P = .54	5.64 ± 6.66 4.29 ± 5.79 U = 25,365.5, z = −2.44 **P = .015**	4.65 ± 5.93 4.64 ± 6.06 U = 11,821.0, z = −0.88 P = .38	5.57 ± 6.77 4.41 ± 5.82 U = 20,228.0, z = −1.58 P = .11	3.76 ± 4.21 5.56 ± 6.78 6.33 ± 7.25 4.08 ± 5.53 χ^2_3 = 11.52 **P = .009**[d]
Psychotic episodes,[e] % yes/% no[b]	46.2/53.8 50.9/49.1 χ^2_1 = 0.96 P = .33	43.5/56.5 50.3/49.7 χ^2_1 = 1.00 P = .32	42.1/57.9 51.8/48.2 χ^2_1 = 3.54 P = .06	48.8/51.2 49.6/50.4 χ^2_1 = 0.01 P = .93	49.4/50.6 49.0/51.0 χ^2_1 = 0.01 P = .94	47.4/52.6 53.1/46.9 37.2/62.8 52.2/47.8 χ^2_3 = 6.85 P = .08[e]
Cannabis abuse,[e] % yes/% no[b]	16.9/83.1 11.3/88.7 χ^2_1 = 3.39 P = .07	18.3/81.7 12.3/87.7 χ^2_1 = 2.02 P = .16	19.7/80.3 10.4/89.6 χ^2_1 = 8.63 **P = .003***	22.2/77.8 11.9/88.1 χ^2_1 = 4.62 **P = .03**	21.4/78.6 11.3/88.7 χ^2_1 = 7.55 **P = .006***	31.8/68.2 21.7/78.3 15.0/85.0 9.8/90.2 χ^2_3 = 14.15 **P = .002***[e]
Alcohol dependence,[e] % yes/% no[b]	9.5/90.5 9.2/90.8 χ^2_1 = 0.01 P = .92	11.1/88.9 8.9/91.1 χ^2_1 = 0.37 P = .55	9.8/90.2 8.8/91.2 χ^2_1 = 0.14 P = .71	14.8/85.2 8.3/91.7 χ^2_1 = 2.59 P = .11	6.7/93.3 9.4/90.6 χ^2_1 = 0.74 P = .39	8.5/91.5 7.8/92.2 13.3/86.7 4.5/95.5 χ^2_2 = 0.66 P = .72[e]

[a]Boldface indicates significance (P < .05); asterisk indicates significance after correction for multiple testing.
[b]Percentages indicated for categorical variables demonstrate those patients with/without the clinical variable or with/without the subcategory of trauma.
[c]Mann-Whitney test.
[d]Kruskal-Wallis test.
[e]χ^2 test.

r^2 = 0.03, P = .011). Also, in males, patients with sexual or emotional abuse presented a higher prevalence of rapid cycling than patients without sexual or emotional abuse; however, for males, this difference reached only trend levels, not statistical significance (sexual abuse: 33.3% vs 16.8%, r^2 = 0.02, P = .07; emotional abuse: 27.7% vs 16.2%, r^2 = 0.02, P = .078). Having said this, the subsample of males with trauma was smaller than the subsample of females with trauma; therefore, the findings should be viewed in light of possible loss of power to detect significant findings in the male group compared to the female group.

Number of depressive episodes was significantly associated with emotional abuse. Stratification by gender showed that females with emotional abuse demonstrated an increased number of depressive episodes compared to females without emotional abuse (mean ± SD number of depressive episodes: 7.07 ± 6.96 vs 4.72 ± 5.44, r^2 = 0.03, P = .002). When we investigated males only, no significant

Figure 1. Childhood Abuse and Age at Onset of Bipolar Disorder[a]



[a]The figure illustrates a dose relationship between childhood abuse and earlier age at onset. The more abuse subtypes the patient reported, the lower the age at onset. Kruskal-Wallis test; $P < .001$; no abuse: n = 361, mean ± SD = 25.76 ± 10.54; 1 abuse subtype: n = 114, mean ± SD = 22.11 ± 9.49; 2 abuse subtypes: n = 61, mean ± SD = 20.54 ± 7.55; 3 abuse subtypes: n = 22, mean ± SD = 19.64 ± 7.05.

difference in the number of depressive episodes was observed in patients with or without emotional abuse (4.67 ± 5.27 vs 3.77 ± 4.40, $r^2 = 0.01$, $P = .25$).

Number of hypomanic or manic episodes was associated (Mann-Whitney test) with increased frequency of emotional abuse, as well as a dose effect of abuse, although the adjusted *P* values were above the cutoff for statistical significance. Also, after we corrected for multiple testing, no significant associations were observed for psychotic episodes.

Significant associations were observed between cannabis abuse and sexual abuse, as well as cannabis abuse and emotional abuse. No significant associations were observed between alcohol dependence and childhood trauma.

Is a Specific Subtype of Childhood Trauma Driving the Association Between Childhood Trauma and Clinical Characteristics?

Multilevel regression analyses were performed to investigate whether specific underlying childhood trauma subtypes were driving the associations with clinical characteristics (Table 3). Only sexual abuse and emotional abuse were independently associated with earlier age at onset. Moreover, as shown in step 2, this association was still significant after gender was added into the model. Emotional and sexual abuse were independently associated with increased frequency of a history of suicide attempt and remained so after gender and duration of illness were introduced into the model. Sexual abuse was the only statistically significant predictor of rapid cycling. Sexual abuse was still associated with rapid cycling after gender and duration of illness were added into the model.

We performed an additional post hoc analysis correcting for recruitment site, as the French sample had a slightly higher number of rapid-cycling subjects than the Norwegian sample, and the Norwegian sample had a slightly lower age at onset than the French sample. Reassuringly, after we corrected for recruitment site, sexual abuse was still significantly associated with rapid cycling ($P = .006$), and sexual abuse ($P = .002$) and emotional abuse ($P = .002$) were significantly associated with earlier age at onset (data not shown). Last, we performed a multivariate analysis controlling for alcohol and cannabis use, and our results remained the same.

DISCUSSION

Our study demonstrated robust associations between a more severe clinical presentation and childhood adverse events in a large, thoroughly described sample of bipolar disorder patients with the use of a broad range of childhood trauma variables, including neglect (both emotional and physical) and emotional, physical, and sexual abuse. Our results show that childhood traumatic events are associated with a more severe form of bipolar disorder characterized by earlier onset of the illness, greater prevalence of a history of suicide attempt, rapid cycling, greater proneness toward depression, and more cannabis use. We found a clear dose-response effect of abuse on all of these clinical variables, in the direction of an association of increased trauma with more severe clinical expression. The current findings also include gender differences, which have not been observed before.

Across clinical characteristics, our results demonstrate that the association of childhood trauma is stronger for abuse (emotional, physical, and sexual) than neglect (emotional and physical). The effect observed for neglect seems to be driven by an underlying effect of abuse, specifically emotional abuse. This suggests that the trauma probably must reach a certain level of intensity (abuse vs neglect and at least a moderate to severe intensity) to have an effect on the phenotype. Indeed, a unidirectional relation can be observed between abuse and neglect, with the abuse increasing the relative risk for being exposed to neglect (the inverse being false). For example, we observed a relationship between neglect and higher prevalence of at least 1 suicide attempt ($P = .02$); however, this effect disappeared when other types of trauma were entered into a multivariate model, and only emotional and sexual abuse remained significantly associated with suicide attempt.

Regarding the effect of individual specific subtypes of abuse, we found that sexual abuse was the strongest predictor of rapid cycling, while both emotional and sexual abuse were related to lower age at onset and to suicide attempts. There are some indications that physical abuse is associated more with psychosis, and emotional abuse, with bipolar disorder, while sexual abuse might be associated more with impulsivity dyscontrol.[1,5] Sexual abuse does not seem to be strongly associated with psychosis,[28] but rather with suicide attempt.[29] Indeed, emotional abuse is increased in patients with bipolar disorder, also after correcting for other types of abuse, compared to healthy controls.[1,5] It might be that emotional abuse is specifically linked to bipolar disorder based on possible links to emotional dysregulation, which is a core symptom of bipolar disorder. We could hypothesize

Table 3. Multivariate Regression Analyses: Childhood Trauma and Clinical Characteristics[a]

	Step 1					Step 2				
Variable	Coefficient	SE	*t*	*P* Value	95% CI	Coefficient	SE	*t*	*P* Value	95% CI
Age at onset[b]										
Constant	3.51	0.07	47.52	< .001	3.37 to 3.66	3.61	0.09	45.26	< .001	3.44 to 3.77
Gender	NA					−0.07	0.03	−2.21	.03	−0.14 to −0.01
CTQ emotional neglect	−0.02	0.04	−0.48	.63	−0.10 to 0.06	−0.03	0.04	−0.65	.52	−0.10 to 0.05
CTQ physical neglect	−0.05	0.05	−0.90	.37	−0.15 to 0.06	−0.04	0.05	−0.77	.44	−0.14 to 0.06
CTQ emotional abuse	−0.13	0.04	−3.06	**.002***	−0.21 to −0.05	−0.13	0.04	−3.03	**.003***	−0.21 to −0.04
CTQ sexual abuse	−0.14	0.04	−3.08	**.002***	−0.22 to −0.05	−0.12	0.04	−2.68	**.008***	−0.21 to −0.03
Goodness of fit					$R^2 = 0.07$					$R^2 = 0.07$
Suicide attempts[c]	B	SE	Wald	*P* Value	OR (95% CI)	B	SE	Wald	*P* Value	OR (95% CI)
Constant	−1.84	0.33	30.62	< .001	0.16	−2.95	0.46	42.11	< .001	0.05
Duration of illness	NA					0.03	0.01	14.78	< .001	1.03 (1.01 to 1.05)
Gender	NA					0.51	0.19	6.90	.009	1.66 (1.14 to 2.42)
CTQ emotional abuse	0.47	0.21	5.15	**.023**	1.60 (1.07 to 2.39)	0.42	0.21	3.97	**.05**	1.53 (1.01 to 2.32)
CTQ sexual abuse	0.59	0.24	6.30	**.012**	1.80 (1.14 to 2.86)	0.47	0.24	3.71	**.05**	1.59 (0.99 to 2.56)
Goodness of fit					$R^2 = 0.04$[d]					$R^2 = 0.09$[d]
Rapid cycling[e]										
Constant	−2.81	0.39	50.78	< .001	0.06	−2.99	0.52	33.40	< .001	0.05
Duration of illness	NA					0.01	0.01	1.32	.25	1.01 (0.99 to 1.03)
Gender	NA					0.05	0.23	0.05	.82	1.05 (0.67 to 1.65)
CTQ emotional abuse	0.47	0.24	3.70	.055	1.60 (0.99 to 2.57)	0.43	0.25	3.06	.08	1.54 (0.95 to 2.48)
CTQ sexual abuse	0.71	0.27	7.20	**.007***	2.04 (1.21 to 3.42)	0.69	0.23	6.53	**.011**	1.99 (1.17 to 3.38)
Goodness of fit					$R^2 = 0.05$[d]					$R^2 = 0.05$[d]

[a]Boldface indicates significance ($P \leq .05$); asterisk indicates significance after correction for multiple testing.
[b]Linear regression.
[c]Logistic regression (0 = no suicide attempts, 1 = suicide attempts).
[d]Nagelkerke.
[e]Logistic regression (0 = no rapid cycling, 1 = rapid cycling).
Abbreviations: CTQ = Childhood Trauma Questionnaire, NA = not applicable.

that emotional abuse and sexual abuse are associated with development of emotional dysregulation, which may be an underlying core link between childhood trauma and increased symptomatology in bipolar disorder patients; the link could be mediated by intermediate dimensions such as increased affective dysregulation[5] or impulsivity.[30] We suggest further investigation of this in future studies.

Females reported greater frequency of trauma, as well as greater associations with clinical characteristics of bipolar disorder, than males. Females with childhood trauma showed stronger associations with earlier onset of illness, rapid cycling, suicide attempts, and more depressive episodes than males with trauma. We therefore performed additional analyses controlling for gender to rule out that female patients drove the association between childhood trauma and the development of more severe clinical characteristics in bipolar disorder. The results remained the same, indicating an additive effect of gender, as well as a significant gender-nonspecific effect of childhood trauma, on clinical characteristics in bipolar disorder.

Lastly, future research should investigate the mechanisms behind associations between childhood trauma and clinical symptomatology in bipolar disorder, such as the link between childhood trauma and substance abuse. As already mentioned, childhood trauma has been related to an increased risk of substance abuse,[31] and patients with bipolar disorder show a higher frequency of substance abuse compared to the general population.[32] In bipolar disorder, substance abuse is associated with increased sensitization and vulnerability to recurrent episodes, thus possibly driving illness progression.[33] It would therefore be of interest to investigate if substance abuse is moderating the effect of childhood trauma on clinical characteristics in bipolar disorder. Moreover, we know that bipolar disorder is highly heritable; to further investigate how genetic variants may moderate the effect of childhood trauma on clinical expressions of bipolar disorder would be of great interest. Bipolar disorder is determined by both genetic and environmental risk factors, with interactions between factors remaining to be clarified.[34] Some attempts have been made to explore such an issue in bipolar disorder with, for example, interactions between *BDNF* gene variants and early life stress on bipolar course.[35] Future studies will focus on identifying how some genetic susceptibility factors are likely to moderate the effects of childhood trauma on the clinical expression of the disorder.

With regard to study limitations, first, data on childhood trauma were, as in most clinical studies of this phenomenon, obtained retrospectively, with the inherent weakness of retrospective reporting designs. However, the retrospective collection of childhood trauma data in patients with severe mental disorders has been found a valid and reliable source of information in previous studies.[2] Our study fulfills the quality criteria of Fisher and Hosang,[16] with the limitation that in the Norwegian sample no standardized assessment, but rather clinical judgment, was used to decide whether patients were in a suitable mood to reliably fill in the CTQ form; all patients from the French sample were systematically evaluated and defined as euthymic at time of assessment. Another limitation of using the CTQ is that it does not identify all types of traumas, such as childhood traumas due to early parental loss, divorce, natural disasters, house fires,

and so on. As a result, these kinds of childhood traumas are left out of the multivariate analysis, yet may explain some of the dependent variables. Also, not assessing for these traumas may lead to misclassification of cases and noncases, with some who may have had 1 or more of these other traumas still being classified as not having an early trauma using the CTQ form. However, although the CTQ has its limitations, it is a well-used questionnaire in the literature, which improves the possibility of comparing findings across studies. We cannot rule out, though, that some patients may have experienced other types of traumas not assessed here.

Moreover, we have previously reported that in bipolar disorder, substance abuse is associated with increased sensitization and vulnerability to recurrent episodes, thus possibly driving illness progression.[33] Substance abuse has also been linked to a possibly worse course of illness (increased risk of suicide, lower age at onset, rapid cycling).[36–38] We also know that there is a high correlation between childhood trauma and substance use,[39,40] and although we performed additional multivariate analyses controlling for lifetime cannabis and alcohol abuse, the association between substance abuse, childhood trauma, and bipolar symptomatology should be further investigated. It may also be that disorders comorbid with bipolar disorder, such as anxiety disorders, are driving some of the effects we see; for example, anxiety disorders have been associated with suicidality.[41] Unfortunately, we do not have complete data on comorbid diagnoses and have therefore not included them as possible confounders in our analyses. Finally, clinical variables were assessed using the SCID-I or the DIGS. Reliability analysis comparing DIGS and *DSM* criteria has shown excellent reliability scores for bipolar disorders,[19] indicating that use of the DIGS did not bias our results.

The main strength of this study is the large sample size, which provided the power to investigate gender differences, as well as made it possible to perform multilevel analyses, in studying individual associations of trauma with clinical characteristics. Lastly, our large study also included measures of neglect and emotional abuse as well as the more frequently investigated sexual and physical abuse, which was an advantage of our study compared to studies in the literature.[15] Our findings have multiple important implications: first, improving the understanding of the clinical heterogeneity of bipolar disorder presentation, and second, identifying those at risk of a more severe clinical picture.

To conclude, the strong associations between reports of childhood trauma and increased symptom levels in bipolar disorder patients observed in this large study support a role of childhood trauma in the development of more severe clinical characteristics in bipolar disorder. The findings further highlight the importance of assessing childhood trauma in bipolar disorder research, which should be systematically included in the clinical assessment of the patients.[42]

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Supplementary Material

Article Title: Childhood Trauma Is Associated With Severe Clinical Characteristics of Bipolar Disorders

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List of Supplementary Material for the article

1. eTable 1 Demographics Comparison Between Sites

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Supplementary eTable 1. Demographics comparison between sites

	French site	Norwegian site	Statistics
Age (mean±SD)	43.50±13.24	33.25±11.67	*t*=8.78, df=585, p<0.001
Gender, M/F	168/250	66/103	X^2=0.07, df=1, p=0.80
Suicide attempts (yes/no)	156/256	55/112	X^2=1.25, df=1, p=0.26
Depressive episodes (mean±SD)	4.57±5.29	5.36±6.02	*t*=-1.44, df=275, p=0.15
Manic/hypomanic episodes (mean±SD)	4.72±6.05	4.35±5.98	*t*=0.66, df=554, p=0.51
Psychotic episodes (Yes/No)	163/181	84/72	X^2=1.79, df=1, p=0.18
Rapid Cycling (Yes/No)	89/297	25/136	X^2=3.90, df=1, p=0.05
Lifetime cannabis abuse (Yes/No)	50/362	25/144	X^2=0.75, df=1, p=0.39
Lifetime alcohol dependence (Yes/No)	30/382	23/146	X^2=5.79, df=1, p=0.016
Age at onset (mean±SD)	25.17±10.32	21.87±9.24	*t*=3.59, df=577, p<0.001
Duration of illness (mean±SD)	18.36±12.41	11.39±10.03	*t*=7.06, df=377, p<0.001
CTQ total score (mean±SD)	41.75±12.89	44.03±16.43	*t*=-1.57, df=237, p=0.12
Diagnosis			X^2=0.61, df=2,
Bipolar 1, n	306	119	p=0.74
Bipolar 2, n	88	38	
Bipolar NOS, n	24	12	

CTQ=Childhood Trauma Questionnaire, F=female, M=male, NOS=not otherwise specified.