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Bruno Etain, Flavie Mathieu, Chantal Henry, Aurélie Raust, Isabelle Roy, Anne Germain, Marion Leboyer, Frank Bellivier

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Running head: Emotional abuse and bipolar disorder

Bruno ETAIN (1,3), Flavie MATHIEU (1), Chantal HENRY (1,2,3), Aurélie RAUST (1,3),

Isabelle ROY (3), Anne GERMAIN (4), Marion LEBOYER (1,2,3), Frank BELLIVIER (1,2,3).

1) INSERM, Unité 955, IMRB, Pôle de Génomique Médicale, Equipe de Psychiatrie Génétique, Créteil, F-94000, France ;

2) Université Paris Est, Faculté de Médecine, IFR10, Créteil, F-94000, France ;

3) AP-HP, Groupe Henri Mondor-Albert Chenevier, Pôle de Psychiatrie, Créteil, F-94000, France ;

4) Department of Psychiatry, University of Pittsburgh School of Medicine, Pennsylvania, USA.

Corresponding author:

Bruno ETAIN, MD, PhD.

Pôle de Psychiatrie

Hôpital Albert Chenevier

40, rue de Mesly

94010 Créteil Cedex - FRANCE

Tel: + 33 1 49 81 32 90

Fax: + 33 1 49 81 30 99

Mail : bruno.etain@inserm.fr

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Abstract

Childhood trauma has been suggested to be involved in the susceptibility to bipolar disorder.

However, case-control studies are lacking, while the preferential implication and the dose-effect

of different trauma subtypes remain poorly investigated. 206 bipolar patients and 94 controls

completed the Childhood Trauma Questionnaire (CTQ). The CTQ total score was higher for

bipolar patients than for controls. The presence of multiple trauma was significantly more

frequent in bipolar patients than in controls (63% versus 33%). Multiple logistic regression

suggested that only emotional abuse was associated with bipolar disorder with a suggestive dose-

effect. Clinical practice should include systematic assessment of childhood trauma among

bipolar patients with a particular focus on emotional abuse.

Introduction

Bipolar affective disorder is a chronic and severe psychiatric disorder of multifactorial origin. More than 20 years after the demonstration of its genetic component, the search for susceptibility genes is still inconclusive (Smoller & Gardner-Schuster, 2007). This may be partly explained by the under-exploration of the environmental aspects of the disease that require to be incorporated in the analysis. Psychological stressors are probably the most promising environmental determinants (Etain, Henry, Bellivier, Mathieu, & Leboyer, 2008) and have been implicated in the onset and recurrences of unipolar and bipolar affective disorders (Cohen, Hammen, Henry, & Daley, 2004; Paykel, 2003; Post, 1992). Most investigations have focused on recent major life events, implicating both acute and chronic stressors while the role of early childhood trauma remains under-explored (Johnson & Roberts, 1995; Paykel, 2003; Rush, 2003).

Childhood traumatic events are more frequently reported by bipolar than by unipolar patients (Hyun, Friedman, & Dunner, 2000). Histories of severe childhood abuse were identified in more than half of the bipolar patients (Garno, Goldberg, Ramirez, & Ritzler, 2005; Maguire, McCusker, Meenagh, Mulholland, & Shannon, 2008). Childhood traumatic events may also modulate the clinical expression of the disorder, being associated with an earlier onset of the disease (Garno et al., 2005), rapid cycling course (Garno et al., 2005; Leverich & Post, 2006), psychotic features (Hammersley et al., 2003), suicidal behavior (Brown, McBride, Bauer, & Williford, 2005; Garno et al., 2005; Leverich & Post, 2006), comorbidities with substances misuse (Brown et al., 2005; Garno et al., 2005; Leverich & Post, 2006) and with panic disorder (Brown et al., 2005). These data thus suggest that childhood trauma may be an associated risk in

bipolar disorder and may also influence its clinical expression and outcome (Etain et al., 2008).

However, many studies in this field have been hampered by methodological limitations, particularly the absence of control groups, but also differences between assessment methods (structured interview versus self-reported measure) and small samples of patients. The preferential implication of some subtypes of trauma also requires further investigation since most studies have considered childhood trauma as a whole or have restricted the investigation to physical and/or sexual abuses (Carballo et al., 2008; Hammersley et al., 2003). Since interaction between a given subtype of trauma with specific genetic factors might be the causal link to a given psychiatric condition (Caspi & Moffitt, 2006), the association between bipolar disorder and different subtypes of trauma requires to be formally tested. Finally, a dose-effect of trauma subtypes has never been investigated in bipolar disorder although this effect has previously been reported in other psychopathological conditions, such as in psychosis (Read, van Os, Morrison, & Ross, 2005).

The aims of this study were thus (i) to retrospectively assess the prevalence and the severity of different subtypes of childhood trauma among euthymic bipolar patients and controls, (ii) to investigate the preferential implication of some trauma subtypes and (iii) to test for their dose-effect.

Method

Participants

Bipolar type I and type II patients (according to DSM-IV criteria (American Psychiatric Association, 1994)) were recruited in two university-affiliated psychiatric departments in France (Paris/Créteil and Bordeaux). Inclusion criteria for bipolar patients were age over 18 years, caucasian and normothymia defined as a Montgomery Asberg Depression Rating Scale and a Mania Rating Scale scores below five (Bech, Rafaelsen, Kramp, & Bolwig, 1978; Montgomery & Asberg, 1979). The control group was composed of blood donors having neither a personal nor a familial (first-degree relatives) history of mood disorders or suicidal behavior .

Measures

All participants were interviewed using the French version (Preisig, Fenton, Matthey, Berney, & Ferrero, 1999) of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) providing lifetime DSM-IV axis I diagnoses (American Psychiatric Association, 1994). To check the inter-rater reliability for DSM-IV axis I diagnoses, the following procedure was applied (Preisig et al., 1999). A team of interviewers (8 psychologists and psychiatrists) was trained over a four month period using videotaped interviews and supervisions with experienced clinicians. All interviewers were blinded as to the referral diagnosis of the subject. Raters performed interviews for the inter-rater and test-retest reliability study in a balanced way, exchanging roles between first-interviewer, observer at the first interview, and retest interviewer. Patients were interviewed by a member of the team in the presence of an observer (co-rater) who simultaneously and independently completed a DIGS. At the end of the interview, interviewer and observer independently assigned DSM-IV lifetime diagnoses. The inter-rater reliability was computed on 136 patients from psychiatric inpatient and outpatient facilities with referral diagnoses of bipolar disorder, major depressive disorder, schizoaffective disorder,

schizophrenia/schizophreniform disorder, alcohol or drug disorder. The inter-rater reliabilities

(kappa coefficients) we achieved for the DIGS were 0.85 for bipolar disorders (Preisig et al.,

1999) and 0.93 for major depressive disorder/dysthymia, this being consistent with the inter-rater

reliabilities of the English version (Nurnberger et al., 1994). The French version of the DIGS has

no specific section to check the presence of posttraumatic stress disorder.

Childhood traumatic events were recorded using the short version of the Childhood

Trauma Questionnaire (CTQ), a 28-item self-report measure developed by Bernstein et al.

(Bernstein et al., 1994). This questionnaire showed excellent test-retest reliability, as well as

convergent and discriminant validity with a structured trauma interview. It has been validated in

clinical and non clinical populations (Bernstein & Fink, 1998). The CTQ yields a total score

(range 25-125) that is recommended to be used as a continuous variable, and five sub-scores

(range 5-25 for each) for neglects (emotional and physical) and abuses (emotional, physical and

sexual) (recommended to be used as categorical variables). Emotional neglect refers to the failure

of caretakers to provide

basic psychological and emotional needs, such as love, encouragement, belonging and support.

Emotional abuse refers to verbal assaults on a child's sense of worth or well-being, or any

humiliating, demeaning, or threatening behavior directed toward a child by an older person.

Physical neglect refers to failure to provide basic physical needs including food, shelter, and

safety.

Physical abuse refers to bodily assaults on a child by an older person that pose a risk of, or result

in, injury. Sexual abuse refers to sexual contact or conduct between a child and an older person,

including explicit coercion.

According to the thresholds provided by Bernstein et al. (1994), each subtype of trauma was categorized across a gradient of four levels of severity, from "no trauma" to 'severe" through low and moderate. In this study, a trauma subtype was considered as present if reaching at least a low level of severity. The French validated version of the CTQ was used in this study (Paquette, Laporte, Bigras, & Zoccolillo, 2004). Bipolar patients' euthymic state was checked using the French versions of the Montgomery Asberg Depression Rating Scale and of the Mania Rating Scale (Bech et al., 1978; Montgomery & Asberg, 1979) before the CTQ completion.

Procedure

For this study, participants who fulfilled inclusion criteria were systematically approached (about 250 bipolar patients and 100 control subjects). More than 80% of approached participants did agree to participate and all of them have then been included in the study. Comparisons between participants and non-participants were not available since French ethical procedures do not allow collecting the characteristics of non participants.

For bipolar patients, normothymia was assessed using the Montgomery Asberg Depression Rating Scale and the Mania Rating Scale with scores requiring to be below five (Bech, Rafaelsen, Kramp, & Bolwig, 1978; Montgomery & Asberg, 1979). Then, the DIGS was completed in order to characterize bipolar disorders and psychiatric comorbidities. Controls were screened for DSM-IV axis I diagnoses using the DIGS and included in this study only if they met the inclusion criteria. They completed the CTQ only if they were free of personal and familial (first-degree relatives) history of mood disorders (major depressive episodes or unipolar disorder) or suicidal behavior and had a Montgomery Asberg Depression Rating Scale and the Mania

Rating Scale scores below five (Bech, Rafaelsen, Kramp, & Bolwig, 1978; Montgomery &

Asberg, 1979).

For all participants, CTQ was completed after the completion of the DIGS. About 5% of

the questionnaires were not included in the analysis since they were not correctly completed

(missing items).

Written informed consent was obtained from all participants. Institutional review board

approval was previously obtained for this study.

Data analysis

CTQ total score was used as a continuous variable representing the global severity of

childhood trauma. Shapiro-Wilk tests were used to test whether the CTQ total scores fitted

normal distributions in each group. If scores were not normally distributed, non-parametric tests

were used and results were reported using the normal approximation of the statistic (z). Exact p-

values were estimated by simulation over 100.000 replicates. All trauma subtypes were

categorized using four levels of severity ("no trauma", "low", "moderate" and "severe") as

defined by Berstein et al. (Bernstein & Fink, 1998). The significance of differences between

groups was assessed using classical chi-squared tests for discrete variables. Spearman

correlations were used to estimate correlation between trauma subtypes. Logistic regression

(simple and multiple), crude and adjusted odds-ratio (OR) and 95% Confidence Interval (95%

CI) were used to test for an association between bipolar/control status and each trauma subtype.

The best model was selected using a classical likelihood ratio test or Akaike criterion. Cochran-

Armitage linearity test was used to test for an association between trauma subtypes and bipolar

disorder. Statistical analyses were performed using the SAS package (version 9.1.2, SAS

Institute®). Bonferroni's correction was used to allow for multiple testing. Given the number of

tests, a p-value equal or lower than 0.003 was considered as significant.

Results

The CTQ was completed by 206 bipolar patients (155 bipolar type I and 51 bipolar type

II) and by 94 control subjects. Age at interview was similar in the two groups ($M = 41.7$, $SD =$

12.6 years for bipolar patients and $M = 41.2$, $SD = 11.9$ years for control subjects , $z = -0.05$, ns).

The sex ratio (men/women) was significantly lower in the bipolar patient group than in the

control group (0.69 versus 1.61 , $\chi^2(1, N = 300) = 11.3$, $p = .0008$). The characteristics of the

samples are detailed in table 1.

The CTQ total score for both bipolar patients and control subjects groups did not fit

normal distributions (Shapiro-Wilk test $p < .0001$ for the two groups). Consequently, non

parametric tests were used to test for differences between bipolar patients and control subjects.

Age at interview and gender had no effect on CTQ total score in the two groups (data available

on request).

The CTQ total score was significantly higher for bipolar patients than for control subjects

(respectively $M = 43.4$, $SD = 13.5$ and $M = 36.3$, $SD = 7.4$; $z = -5.02$, $p < .0001$).

No category of trauma was more frequent for women than for men in either group, except a trend for sexual abuse in the bipolar sample (presence in 37.7% of women versus 24.4% of men $\chi^2(1, n = 206) = 6.15$, $p = .01$). Therefore, analyses were not stratified by gender.

The prevalence of each subtype of trauma are given for bipolar patients and controls in table 2. Frequency distributions between bipolar patients and controls were significantly different only for emotional abuse, but not for emotional neglect, physical neglect, physical abuse or sexual abuse.

The presence of multiple trauma (at least 2 subtypes of at least a low intensity) was significantly more frequent in bipolar patients than in controls (63.09% versus 32.98% ; $\chi^2(1, N = 300) = 23.56$, $p < .0001$; OR = 3.48, 95% CI = 2.08 - 5.82). The higher the cumulative number of trauma was, the higher the proportion of bipolar patient in a category (Cochrane-Armitage linear tendency test $z = -4.52$, $p < .0001$).

The five subtypes of trauma were correlated as presented in table 3. Simple logistic regression was performed including the five subtypes of trauma independently; then multiple regression was used including the five subtypes of trauma (full model). Logistic regression analysis results are presented in table 4. The best model includes only emotional abuse as an explanatory variable. Likelihood ratio test of the full model versus emotional abuse only was similar ($\chi^2 (4, N = 300) = 6.4$, ns). Emotional abuse was associated with bipolar status when considering the most parsimonious model ($p < .0001$).

Finally, the Cochran-Armitage linear trend showed that the higher the emotional abuse severity was, the higher the proportion of bipolar patients in the group across the gradient of severity, as shown in figure 1.

Discussion

Euthymic adult bipolar patients experienced more severe and more frequent childhood traumatic events than control subjects. More than half of our bipolar sample reported childhood trauma, this being consistent with several previous studies (Garno et al., 2005; Leverich et al., 2002; Maguire et al., 2008). This study is the first to investigate five trauma subtypes frequency and severity in a case-control design, and to test for their preferential implication and dose-effect. The association between childhood trauma and bipolar disorder is mainly due to the over-representation of emotional abuse in patients with a dose-effect relationship. This is consistent with previous studies showing a dose-effect association between childhood trauma severity and various psychiatric disorders during adulthood (for review see (Read et al., 2005)). Our results thus suggest that, among trauma subtypes, emotional abuse may be preferentially associated with bipolar disorder.

This study has several strengths: the comparison with a control group that has been screened for personal and first-degree relatives history of psychiatric disorders and the use of a reliable, validated trauma questionnaire that provides information about trauma frequency and severity and allows fine-grained analysis for trauma subtypes and dose-effect. Nevertheless, this study design also has several limitations.

First, the retrospective assessment of traumatic events during childhood may be

influenced by uncontrolled recall bias although reports on trauma by psychiatric patients were

suggested as remarkably reliable (Meyer, Muenzenmaier, Cancienne, & Struening, 1996). A

recall bias in trauma assessment due to time elapsed since exposure is unlikely in our study (no

correlation between CTQ total score and age at interview in both groups, no correlation between

CTQ total score and duration of illness or the number of major episodes among bipolar patients;

data not shown). Furthermore, the CTQ is a reliable, valid trauma questionnaire and its

psychometric properties have shown high levels of face validity, internal consistency, test-retest

validity and good convergent validity with structured interviews (Bernstein & Fink, 1998;

Bernstein et al., 1994; Bernstein et al., 2003; Paivio & Cramer, 2004). Nevertheless and ideally,

external sources of information should have been used to check validity.

In this study, the history of trauma was assessed during euthymic states in order to avoid

recall bias due to current mood symptoms that may lead to under or over report traumatic

experiences. Nevertheless, the potential influence of residual symptoms cannot be completely

ruled out. Finally, groups were not matched for gender and this may have influenced the findings,

although no effect of gender on the CTQ total score was observed.

The high prevalence and the severity of childhood emotional abuse in our sample could be

interpreted in several ways, nevertheless with caution. Emotional abuse might be regarded as a

potential risk factor for developing bipolar disorder. Indeed, childhood trauma might show long-

lasting effects on catecholamine response to psychological stress (Otte et al., 2005; Roy, 2002),

on corticotropin-releasing factor systems hyper-reactivity (Heim & Nemeroff, 2001; Heim et al.,

2002) and might alter function and structure of medial prefrontal cortex and hippocampus

(Bremner, 2002). All these neurobiological changes might lead to inadequate emotional

regulation (Kooiman et al., 2004; Nemeroff, 2004), thus favoring the emergence of the disorder,

for example by revealing a pre-existing genetic susceptibility or by interacting with other

environmental stressors (Caspi & Moffitt, 2006).

The elevated CTQ score observed among bipolar patients may also be regarded as a consequence

of behavioral disturbances associated either with an early onset of the disease, with prodromal

features (existing before the adulthood onset of bipolar disorder) or with early onset comorbid

disorders. For example, early onset bipolar disorder has been associated with conduct disorder,

disruptive behavior disorders (Biederman et al., 2000; Spencer et al., 2001), attention deficit with

hyperactivity (Kent & Craddock, 2003) and substance abuse comorbidity (Lin et al., 2006). These

clinical features might induce dysfunctional parental attitudes and this burden is likely to lead to

inappropriate discipline and in certain conditions to abuse. Furthermore, caregivers of bipolar

patients exhibit high levels of expressed emotion, including critical, hostile, or over-involved

attitudes (Heru & Ryan, 2004; Ogilvie, Morant, & Goodwin, 2005; Perlick et al., 1999; Romero,

Delbello, Soutullo, Stanford, & Strakowski, 2005). Finally, the association between emotional

abuse and bipolar disorder might be related to parental psychopathological traits. Indeed,

epidemiological studies have shown that affective disorders and alcoholism are more prevalent

among relatives of bipolar children than other children (Smoller & Finn, 2003; Todd, Geller,

Neuman, Fox, & Hickok, 1996). This high prevalence might result in less cohesive and

organized, and more conflictual families (Chang, Blasey, Ketter, & Steiner, 2001; Romero et al.,

2005), in turn resulting in an increased likelihood of traumatic events during childhood.

Childhood trauma, in particular emotional abuse, has also been reported in recurrent

unipolar depression (Bernet & Stein, 1999; Moskvina et al., 2007), thus our results are probably

not specific to bipolar disorder. This potentially shared environmental factor has been supposed

to be associated with heightened emotional stress reactivity (Glaser, van Os, Portegijs, & Myin-

Germeys, 2006), that might be a common feature between bipolar disorder and unipolar recurrent

depression (Hlastala et al., 2000; Myin-Germeys et al., 2003). Our findings may shed some light

on common psychopathological dimensions in unipolar and bipolar disorders in relation with

shared early environmental stressors. This remains speculative and should be formally tested in

samples including both bipolar and unipolar patients.

If confirmed, the preferential association between childhood emotional abuse and bipolar

affective disorder during adulthood may have several clinical implications. First, histories of

childhood trauma required to be routinely assessed in clinical practice among bipolar patients.

Unless trauma histories are systematically assessed, they are unlikely to come to the attention of

treatment professionals (Bernstein & Fink, 1998). A systematic assessment may dramatically

improve the detection of such traumatic events.

The potential therapeutic implications are of major importance (Celano & Rothbaum,

2002; Putnam & Hulsmann, 2002). First, trauma-focused psychotherapies, using different

theoretical models, have been suggested to produce clinical benefits in different subgroups of

patients with history of childhood abuse (Azar & Weinzierl, 2005; Callahan, Price, & Hilsenroth,

2004; Celano & Rothbaum, 2002; Mueser et al., 2007; Price, Hilsenroth, Petretic-Jackson, &

Bonge, 2001; Wheeler, 2007). To date, no substantial evidence exists that such treatment

modalities are effective in bipolar patients with prior abuse and further researches are required in

this field. Since childhood trauma are supposed to increase stress sensitivity and reactivity

(Glaser et al., 2006; Heim et al., 2000; Shack, Averill, Kopecky, Krajewski, & Gummattira,

2004), we may postulate that some psychotherapeutic approaches might target these potential late

consequences of early trauma. This is of great interest since stress reactivity was supposed to be

associated with a greater proneness toward relapses (Hlastala et al., 2000; Myin-Germeys et al.,

2003; Post & Leverich, 2006). However, such hypothesis requires further investigation.

Conclusion

       Bipolar patients reported more frequent and more severe forms of childhood trauma than

controls. This result suggests that childhood trauma might represent a risk factor to bipolar

disorder, although without definitively demonstrated causality. These findings involve that

clinicians should be aware of such environmental risk factors and routinely evaluate histories of

childhood trauma among bipolar patients. This potentially leads to trauma-focused therapeutic

interventions in patients with such past history. We report for the first time a preferential

implication and a dose-effect of childhood emotional abuse in bipolar patients, which may

represent either a specific risk factor or a characteristic correlated with other risk factors in

offspring such as familial/genetic susceptibility factors or parental psychopathology. Further

case-control studies and high risk studies are required to replicate these findings and to

investigate the preferential implication of emotional abuse in bipolar disorder.

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Table 1 : Demographic and clinical characteristics of bipolar patients ($n = 206$) and control

subjects ($n = 94$)

Group	Bipolar patients	Control subjects
Sex ratio (men/women) *	0.69 (84/122)	1.61 (58/36)
Age at interview M (SD)	41.7 (12.6)	41.2 (11.9)
Bipolar disorder type I	75.2%	0%
Age at onset M (SD)	23.9 (9.3)	-
Duration of illness M (SD)	17.8 (11.2)	-
Family history of bipolar disorder	46.9%	0%
Psychotic symptoms (lifetime presence)	57.1%	0%
Suicide attempt (lifetime presence)	40%	0%
Panic disorder (with or without agoraphobia)	19.9%	0%
Social phobia	10.4%	0%
Generalized anxiety disorder	10.8 %	0%
Alcohol or cannabis abuse/dependence	30.7%	0%

* $p < .0001$

The presence of posttraumatic stress disorder is not available (absence of specific section in

the French version of the DIGS)

Table 2 : Comparison between bipolar patients (*n* = 206) and controls (*n* = 94) for the

prevalence of each childhood trauma subtype categorized along a gradient of 4 severity levels

Trauma subtype	Group	None	Low	Moderate	Severe	p_{exact}
Emotional neglect	Bipolar	15.53%	45.63%	22.82%	16.02%	.03
	Controls	23.40%	54.26%	14.89%	7.45%	
Emotional abuse	Bipolar	50.97%	24.27%	9.71%	15.05%	3.10^{-5}
	Controls	76.60%	18.09%	3.19%	2.12%	
Physical neglect	Bipolar	72.81%	17.48%	5.34%	4.37%	.01
	Controls	87.23%	7.45%	5.32%	0.00%	
Physical abuse	Bipolar	77.67%	12.14%	5.34%	4.85%	.04
	Controls	91.49%	5.32%	2.13%	1.06%	
Sexual abuse	Bipolar	68.93%	11.17%	9.71%	10.19%	.10
	Controls	80.86%	9.57%	6.38%	3.19%	

Table 3 : Spearman correlations among the five trauma subtypes in the whole sample (pooling

bipolar patients and controls, *N* = 300)

Trauma subtypes	Emotional abuse	Physical neglect	Physical abuse	Sexual abuse
Emotional neglect	.51 **	.50**	.31 **	.18 *
Emotional abuse	-	.39 **	.53 *	.38 **
Physical neglect	-	-	.30 **	.21 *
Physical abuse	-	-	-	.44 **

** p < .0001 ; * p < .002

Table 4: Results of logistic regressions testing for an association between disease status and the five trauma subtypes

	Simple logistic regression						Multiple logistic regression (-2 log L) = 340.59				
	B	*SE B*	*p value*	*-2 Log L*	Crude OR	95% CI	*B*	*SE B*	*p value*	Adjusted OR*	95% CI
Emotional neglect	0.44	0.15	.003	362.04	1.56	1.16-2.08	0.08	0.18	.63	1.09	0.77-1.54
Emotional abuse	0.76	0.18	<.0001	346.98	2.15	1.52-3.04	0.63	0.21	.003	1.88	1.23-2.86
Physical neglect	0.57	0.23	.01	365.26	1.77	1.13-2.78	0.25	0.25	.32	1.28	0.79-2.10
Physical abuse	0.65	0.25	.01	363.95	1.92	1.17-3.16	0.02	0.31	.95	1.02	0.56-1.88
Sexual abuse	0.39	0.16	.01	362.88	1.47	1.09-2.00	0.16	0.18	.36	1.18	0.83-1.67

* Adjusted OR correspond to the stratified estimate of the odds ratio adjusted for the four other CTQ traumas.

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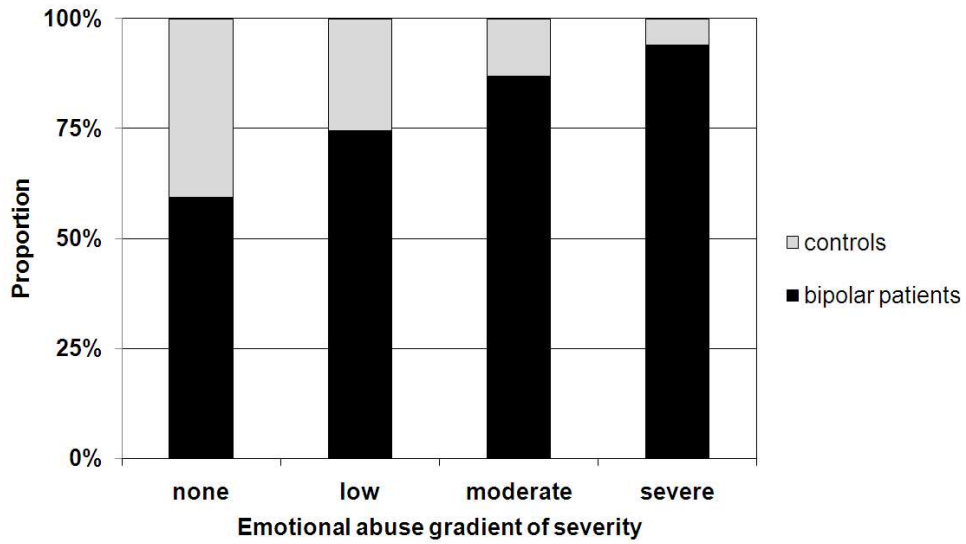51
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Figure 1 : Proportion of bipolar patients (n = 206) and controls (n = 94) for each emotional abuse
severity level (none, low, moderate, severe)
305x174mm (96 x 96 DPI)