Beyond genetics: childhood affective trauma in bipolar disorder

Identification of the pathophysiological determinants of bipolar disorder is a major challenge with implications for the early detection, prevention, and treatment strategies of this disorder. The strong heritability of bipolar disorder led researchers to focus principally on biological and genetic determinants. However, more than 20 years after the demonstration of this genetic component, the search for susceptibility genes remains inconclusive, due to conflicting results obtained by association and linkage studies. One of the many reasons

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for this is probably the underexploration of environmental aspects of the disease, which remain poorly understood. Childhood traumatic events are probably the most promising environmental determinant to have been investigated. This paper will review the arguments in favor of the association between childhood trauma and bipolar disorder and will discuss the interpretations of such observations. We will also present new data in this field and propose a strategy for further, more precise exploration of this environmental factor and its interaction with susceptibility genes.

Genetics in bipolar disorder: a never-ending story

Bipolar affective disorders (BPAD) have well-documented genetic determinants, as demonstrated by family, twin, and adoption studies (1). Since the 1980s, molecular biologists have begun to unravel the genetic factors conferring susceptibility to bipolar disorder. Despite the demonstrated high heritability of bipolar disorder, only a few genes have yet been identified. Linkage and association studies have produced conflicting results. Several complementary approaches have been proposed to facilitate the identification of susceptibility genes in bipolar disorder and to improve our understanding of its etiological determinants.

The first of these approaches aimed at selecting appropriate genetic strategies for the analysis of complex disorders. Classically, the ‘pure genetic’ approach is based on the use of linkage and association studies to localize susceptibility genes. Classical genome scan methods based on microsatellites have often given disappointing results, and meta-analyses of published genome-wide searches have failed to produce highly significant evidence of linkage (2). Genetic studies based on candidate genes have also failed to demonstrate any strong association with bipolar disorder. Even for genes identified as pathophysiological candidates in bipolar disorder [such as the genes encoding brain-derived neurotrophic factor (3), serotonin transporter (4), monoamine oxidase A (5), tyrosine hydroxylase (5), or dopamine receptor types 3 and 4 (6, 7)], no strong association with the disease has been demonstrated. The lack of replication of results has been accounted for by the use of invalid phenotypes, sample heterogeneity, and unknown genetic parameters, such as valid models of inheritance to be used in parametric analyses (8). The emergence of whole-genome association studies (9, 10) has raised hopes that the genes involved in bipolar disorder may be characterized in the near future.

The second approach is closer to the clinical specificities and disparities of the disorder and involves the use of two complementary strategies to define basic phenotypes more accurately. One of these strategies aimed at the identification of specific subforms of the disorder, the ‘candidate symptom approach,’ whereas the other involves the characterization of susceptibility traits, or endophenotypes, in healthy relatives of affected individuals (11, 12). These approaches narrow down diagnostic entities, rendering them more homogeneous and, presumably, more likely to have a simpler genetic basis. The candidate symptom approach has led to the identification of subforms of bipolar disorder, such as early-onset bipolar disorder (13), resulting in the identification of narrow linkage regions (14). However, narrowing down the phenotype into more homogeneous subtypes is probably insufficient to unravel genetic background in bipolar disorder.

Back to nurture

A third approach has therefore been developed, involving the incorporation of information about environmental factors into the pathophysiological model of the disorder. Even the most heritable psychiatric disorders, including bipolar disorder (1), schizophrenia (15), and obsessive-compulsive disorder (16), are thought to have a multifactorial origin, with genetic and non-genetic factors probably interacting. These gene–environment interactions assume that environmental factors are major causes of the disorder, whereas genes affect the level of susceptibility to these factors (17). Genotype was first shown to affect the ability of an environmental risk factor to bring about mental disorders in 2002, by Caspi et al. (18), who showed that a functional polymorphism in the gene encoding monoamine oxidase A modulates the effect of childhood maltreatment on the development of antisocial problems. Other supportive evidence has been obtained, suggesting that interactions between the catechol-O-methyl transferase (COMT) gene and adolescent cannabis use affect adult psychosis (19), interactions between the serotonin transporter gene and life events affect depression and suicidality (20), and interactions between the COMT gene and herpes simplex virus type I infection affect cognitive impairment in bipolar disorder (21).

Data concerning the effects of environmental factors on bipolar disorder remain very scarce, although several environmental factors have been identified as potentially involved in this disorder.
These factors include early childhood trauma (22–27), stressful life events (28), virus infections (21, 29–31), cannabis use (32, 33), obstetric complications (34), and even very distant environmental factors, such as solar cycles (35). History of childhood affective trauma is probably the most widely studied environmental factor in bipolar disorder.

**Childhood trauma in bipolar disorder: the usual suspect**

Childhood traumatic events are frequently reported by bipolar patients (36, 37), more than by unipolar patients (38). Garno et al. (23) identified histories of severe childhood abuse in 51% of a cohort of 100 adults with bipolar disorder, emotional abuse being the most frequent type of trauma. This type of trauma was reported by 37% of bipolar patients, with 24% reporting physical abuse, 24% emotional neglect, 21% sexual abuse, and 12% physical neglect. The different types of trauma were inter-related, one-third of bipolar patients having experienced two or more different forms of trauma.

In a retrospective study, we found that childhood trauma was more frequent and severe in patients with bipolar disorder than in healthy subjects (39). The Childhood Trauma Questionnaire (CTQ) (40), a self-report measure yielding a total score and five subscores (emotional and physical neglect, emotional, physical, and sexual abuse), was completed by 206 euthymic bipolar patients and 94 healthy subjects. The severity and frequency of childhood trauma were compared between bipolar patients and control subjects and the influence of childhood trauma on the course and clinical expression of bipolar disorder was also investigated. CTQ total score was significantly higher for bipolar patients than for healthy subjects (p < 0.0001). More than half of the bipolar patients (54.4%), but only 31.9% of control subjects, had experienced at least one type of trauma (p = 0.0003). Emotional abuse was the only subtype of trauma more frequent in the bipolar patient group than in the control group (p < 0.0001). Having suffered two or more types of trauma was associated with a tripling in the risk of bipolar disorder [odds ratio (OR) = 3.14 (1.52–6.47), p = 0.001].

An association between bipolar disorder and childhood trauma has been demonstrated in several studies, using various methods to assess traumatic events, including retrospective self-reports and questionnaires. However, few well-designed case/control studies have investigated whether childhood trauma (and which specific subtype, if any) may be considered a risk factor for the development of bipolar disorder.

**Childhood trauma and the many facets of bipolar disorder**

Several lines of evidence suggest that childhood trauma not only predisposes subjects to bipolar disorder, but also modulates the clinical expression and course of the disease. Traumatic childhood events may modulate the clinical expression of the illness, resulting in an earlier onset of disease (23), a rapid cycling course (23, 26), psychotic features (24), suicidal behavior (23, 26, 41), comorbid substance misuse (23, 26, 41), and panic disorder (41). Neria et al. (42) showed that a history of physical and sexual abuses in childhood might also affect the remission of bipolar disorder after a first psychotic episode, exposed bipolar patients having more severe symptoms 24 months after onset.

In a sample of 201 bipolar patients (39), we found a correlation between early age at onset and CTQ total score (rho = −0.16, p = 0.02), this correlation being particularly strong for emotional abuse (rho = −0.17, p = 0.01) and sexual abuse (rho = −0.22, p = 0.002). We also demonstrated that high CTQ total score was associated with suicidal behavior in bipolar disorder (p = 0.03). Suicidal bipolar patients more frequently report emotional and sexual abuses (respectively, p = 0.03 and p = 0.04). Having suffered both types of abuse is associated with a doubled risk of suicide attempt among bipolar patients [OR = 2.71 (1.07–6.86), p = 0.04]. Investigations of other subgroups of patients did not replicate the reported associations between childhood trauma and psychotic features, rapid cycling status, comorbidity with substance misuse, or panic disorder.

These results suggest that childhood trauma is associated with a more severe clinical expression and course of the disease. However, the influence of trauma on the affective functioning of bipolar disorder between episodes remains unknown.

**An insidious influence on affective dimensions between episodes**

Most studies have been restricted to the investigation of the role of childhood trauma on the clinical expression of bipolar disorder. However, childhood trauma may also have a more insidious influence on the interepisode affective functioning of bipolar patients, which in turn may affect the overall prognosis of the disease.
We tested this hypothesis, using the Affective Lability Scale (ALS) (43) and the Affect Intensity Measure (AIM) (44) on the same sample of 201 euthymic bipolar patients. The ALS is a self-report scale measuring subjects’ perception of their ability to shift from what they consider to be their normal (euthymic) mood state to anger, depression, elation, and/or anxiety. It also assesses their tendency to oscillate between states of depression and elation, and between states of anxiety and depression. The AIM is a self-report scale measuring individual differences in the intensity of response to a given level of emotion-provoking stimulation. In this sample, CTQ total score was strongly correlated with ALS (rho = 0.33, p < 0.0001) and AIM (rho = 0.23, p = 0.001) scores. These correlations seemed to be mainly due to a correlation between emotional abuse and ALS (rho = 0.35, p < 0.001) and AIM (rho = 0.33, p < 0.001) scores (39). These results may be of prime importance, as they shed light on previous interpretations concerning the relationship between childhood trauma and the clinical expression of bipolar disorder.

In a preliminary study, Henry et al. (45) demonstrated that euthymic bipolar patients reported a higher affective lability and affect intensity than healthy subjects. High scores in affective dimensions were associated with a higher risk of psychiatric DSM-IV Axis I comorbidity, an earlier onset of the disease and a more severe course, with more relapses. The authors concluded that affective lability and affect intensity were core dimensions of bipolar disorder during euthymic periods, suggesting that bipolar disorder is not restricted to mood episodes, but affects specific emotional features between acute episodes. These core affective dimensions may be mainly determined by childhood trauma and are likely to influence the overall prognosis of bipolar disorder.

Taking these results into account, it could be argued that the relationship between childhood trauma, earlier onset, rapid cycling, and comorbidity is mediated by an increase in interepisode affective lability and affect intensity. It is noteworthy that this interpretation does not completely rule out a recall bias in which emotionally unstable adults (i.e., having an elevated score on the ALS and/or the AIM) might be more likely to report emotional abuse than would emotionally stable adults.

The unsolved chicken and egg debate

The high incidence and severity of childhood trauma in bipolar disorder was initially seen as causal, particularly as emotional abuse seems to be the subtype of trauma most frequently associated with bipolar disorder. Early disturbances in emotional and affective interactions between parents and their offspring may predispose the latter to more emotional and affective disturbances in adulthood, suggesting that childhood psychopathology (and perhaps bipolar disorder) result from the child’s environment. It has been shown that those caring for bipolar patients have high levels of expressed emotion, including critical, hostile, or overinvolved attitudes (46–48), and this burden may lead to inappropriate discipline and emotional abuse. However, other interpretations are possible.

Being predisposed to bipolar disorder (even if disease onset has not yet occurred) may increase the likelihood of experiencing trauma during childhood. According to this hypothesis, high CTQ scores may be a consequence of childhood behavioral disturbances linked to an early onset of bipolar disorder, to prodromal features of adult-onset bipolar disorder, or to early comorbid disorders. For example, early-onset bipolar disorder has been associated with comorbid conduct disorder, disruptive behavior disorders (49, 50), attention deficit with hyperactivity (51), and substance abuse (52). All of these clinical features may lead to dysfunctional attitudes in parents.

Alternatively, the genetic characteristics and psychopathology of the parents might lead both to disease in their offspring (because of intrafamilial resemblance) and to an increase in the likelihood of childhood trauma. In this interpretation, ‘the genetic substrate of the parents leads to both the abuse and to the illness in the children’ (53). Thus, genetic loading might contribute to creating an environment in which abuse is more likely to occur. Indeed, epidemiological studies have shown that affective disorders and alcohol misuse are more prevalent among the relatives of bipolar children than among those of other children (1, 54). This high prevalence may result in less cohesive and less organized, more conflictual families (55, 56), in turn resulting in more traumatic events during childhood.

Finally, the hypothesis of an intergenerational transmission of childhood trauma in bipolar families might help the interpretation of the association between traumatic events and the disease. To our knowledge, this has never been investigated in bipolar disorder. This controversial subject explores the hypothesis that the parents’ own history of childhood trauma may drive inadequate parenting attitudes (57, 58) and that the resulting environment may then be more likely to expose children to neglect and/or abuse. Although there is a widespread belief that maltreatment might be
Childhood trauma in bipolar disorder

Direct and/or indirect influence on disease expression?

All the clinical characteristics associated with childhood trauma also have been shown to be related to an earlier onset of the disease. Indeed, early-onset bipolar disorder is a severe form of the disease, characterized by frequent psychotic features, more mixed episodes, high levels of suicidality, a rapid cycling course and high levels of psychiatric comorbidity (with panic disorder and alcohol/drug misuse in particular) (13, 52). Childhood trauma may, therefore, increase the severity of bipolar disorder by lowering the age at onset of the disease and, therefore, inducing a more severe clinical profile.

Beyond this global interpretation, the association between childhood trauma and suicidal behavior deserves specific consideration. Consistent with previous studies (23, 26, 41), we showed that childhood trauma, and more specifically emotional and sexual abuse, increased the risk of suicidal behavior in bipolar patients. This observation is certainly not specific to bipolar disorder, as several recent investigations have shown that early childhood trauma is associated with an increase in the risk of suicidal behavior in patients with schizophrenia (60), alcoholism (61), personality disorders (62), or substance abuse (63), and even in subjects from the general population (64–66). This suggests that the link between childhood trauma and suicidal behavior may be independent of Axis I or II diagnoses.

The association between childhood trauma and alcohol misuse is probably as nonspecific as the association with suicidal behavior, and may be interpreted in a similar manner. It has been shown that childhood trauma, and physical or sexual abuse in particular, are associated with alcohol misuse, demonstrating that this link is not specific to bipolar disorder (67–69). The same observation has also been reported with psychotic features: the association between hallucinations and childhood trauma may be observed not only in bipolar disorder, but also in other psychiatric disorders (24, 70).

Based on these data, the influence of childhood trauma on the clinical expression of bipolar disorder may be seen as involving two types of link. For suicidal behavior, substance misuse, and psychotic features, childhood trauma may have a direct and probably nonspecific effect, as this effect seems to be independent of the psychiatric disorders. Nevertheless, this direct link may be reinforced by an earlier onset of the disease. For other clinical components, the effects of childhood trauma may be mediated by an earlier age at onset (rapid cycling or comorbid panic disorder, for example).

Critical period, vulnerable brain

Childhood is a period of great vulnerability, as the maturation of the central nervous system is highly sensitive to environmental factors. From the postnatal period until the age of seven years, several critical processes affecting cognitive function and emotional regulation take place (proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis) (71, 72). Cognition and emotional regulation continue to mature into adulthood (73). Bipolar disorder is not considered to be developmentally related, unlike schizophrenia, for example, but may nonetheless be partly determined by early changes in brain structures (74). Early life events or stressors may alter the organization of brain development, these changes probably depending on the severity and chronicity of the events concerned.

Early stressors may have a developmental influence on affective lability. Affective stabilization is generally thought to occur gradually during development. It has been suggested that the reactions of children to environmental stimuli become more predictable and stable as they mature cognitively, socially, and morally. Inappropriate rewards and parental attitudes during childhood may induce affective dysregulation in the developing child. This hypothesis is supported by the major contribution of a history of emotional abuse to the observed correlation and is probably not specific to bipolar disorder, as similar results were obtained for patients with personality disorders (75).

However, links between childhood trauma and affective lability in adulthood should not necessarily be interpreted in a strictly linear fashion. MacKinnon et al. (76) have proposed a theoretical model for the development of rapid cycling and borderline personality based on mood instability. This model could shed some light on our results. Genetic factors and brain structural and/or functional abnormalities may predispose the developing child to mood instability. This affective dimension and associated behavioral disturbances may lead to inconsistent or maladaptive parenting styles (resulting in emotional abuse). Inappropriate attitudes on the part of parents or caregivers may then lead to changes in reactivity to external and/or internal stimuli, reinforcing affective instability. Our results may be considered in the context of this developmental model.
Beyond this neurodevelopmental interpretation, previous studies demonstrated that childhood trauma has long-lasting effects on the catecholamine response to psychological stress (77, 78) and on the hyper-reactivity of corticoid-releasing factor systems (79, 80) and may alter function and structure of the medial prefrontal cortex and hippocampus (81). These neurobiological changes may underlie an increase in the risk of bipolar disorder, with childhood trauma leading to inadequate affective regulation (82). However, no study has definitively demonstrated etiological causality between childhood trauma and bipolar disorder.

The tortuous route to childhood trauma/gene interactions in bipolar disorder

Multifactorial disorders, such as bipolar disorder, result from the interaction between small-effects genetic and environmental risk factors (17). Several studies have shown that the effect of exposure to an environmental stressor (or pathogen) on a given psychiatric disorder is conditional on the individual's genotype. Childhood traumas are among the most promising environmental factors meriting further investigation in several psychiatric disorders (18, 20). The identification of childhood trauma as a potential risk factor and/or course disease modifier in bipolar disorder (not only in terms of comorbid conditions, but also in terms of affective functioning) may improve our understanding of the complex interactions between genetic susceptibility factors and the environment.

Currently, there are no specific investigations of the interaction between candidate genes and childhood trauma in the susceptibility to bipolar disorder per se. However, preliminary results in bipolar disorder studies have shown gene-environment interactions on some psychological or neurocognitive dimensions in bipolar disorder. A functional polymorphism of the COMT gene interacts significantly with CTQ total score to impact perceived dissociation (37), and the low-activity Met allele of the brain-derived, neurotrophic factor (BDNF) gene and e4 allele of the apolipoprotein E gene interact with sexual abuse scores to result in reduced memory test performance (83). In a preliminary study, we showed that age at onset and CTQ total score were correlated only in 5HTTLPR ‘ss’ homozygous bipolar patients (\( \rho_{ss} = -0.51, p = 0.002 \) versus \( \rho_{bs+ll} = -0.007, p = 0.94 \)). Emotional neglect was identified as the potentially most important subtype of trauma, as a significant negative correlation was found between age at onset and this subscore only in 5HTTLPR ‘ss’ bipolar patients (\( \rho = -0.59, p = 0.0004 \)) (39). Although preliminary, these results suggest interaction between serotonin transporter gene variants and childhood trauma in bipolar disorder.

Before exploring childhood trauma/gene interactions in bipolar disorder, the following issues need to be considered (84):

(i) Case/control studies with an appropriate design are required for further investigation of the association between childhood trauma and bipolar disorder. Many studies in this field have been hampered by methodological limitations, particularly the absence of a control group and the use of non-validated trauma assessment tools.

(ii) The respective influence of each subtype of childhood trauma needs to be assessed. In bipolar disorder, emotional abuse and/or neglect seem to be the most relevant types of trauma. It remains unclear whether a specific type of trauma is more likely to induce specific psychiatric disturbances, such as sexual abuse for borderline personality (85) or physical abuse for schizophrenia (86).

(iii) The specificity of the association between childhood trauma and bipolar disorder requires further investigation in other clinical samples, as it is certainly not restricted to bipolar disorder, but is observed in almost all psychiatric disorders: schizophrenia (86), substance misuse (87), and personality disorders (88).

(iv) The debate about the most valid way to assess trauma (heteroquestionnaire versus self-reports, retrospective assessment versus prospective follow-up) remains heated. The CTQ is a reliable, validated mode of assessment providing information about trauma frequency and severity and subtypes of trauma (40, 89), but other tools exist and no consensus has been reached as to the gold standard (90). It has been suggested that subjects may be less likely to under- or over-report trauma in self-report questionnaires. Further methodological studies are needed to determine more accurately the reliability and validity of different trauma assessments (91). Although the trauma reported by psychiatric patients appears to be remarkably reliable (92), retrospective assessments of traumatic events during childhood may be influenced by uncontrolled recall bias.

(v) The influence of residual mood symptoms must also be clarified when assessing trauma in bipolar patients. Current mood state or
residual symptoms may lead bipolar patients to under- or over-report childhood trauma.

(vi) Under a developmental hypothesis, some particular types of trauma may have different effects depending on the period of childhood in which they occurred (93). For example, the CTQ gives no information about the timing of different kinds of trauma and does not allow detailed analyses of exactly when traumatic events occurred during the subject’s childhood. This may be of particular relevance, as traumatic events may occur at different stages of central nervous system development. Moreover, the question of a ‘dose response’ should be discussed. It has been consistently shown that the severity of the trauma is directly related to severity of outcome and that the response to adverse childhood experiences increases in a graded fashion (94).

(vii) The influence of childhood trauma on psychological dimensions in bipolar disorder may not be restricted to affective lability and affect intensity measures. For example, other dimensions should be investigated, as childhood trauma may have a role in impulsivity, hostility, and aggression. This association may facilitate interpretation of the links between trauma and suicidal behavior (95, 96).

(viii) The respective roles of parental mental illness and trauma require further attention, and intergenerational studies of childhood trauma are warranted in bipolar families (97).

(ix) Further prospective follow-up of general population or of high-risk cohorts should be discussed, although many already have been set up (18, 97, 98). For example, among the general population, it will be useful to further assess the specificity of subforms of trauma on the outcome of exposed individuals, not only in terms of modifying the risk of different psychiatric disorders but also of various psychopathological traits, such as impulsivity, suicidality, affective lability, or psychosis proneness, that may in turn influence the phenotypic expression of affected subjects. Another purpose of prospective studies might be to follow up children of bipolar parents to investigate the intergenerational aspects of trauma, the prevalence of trauma in children of affected parents, and the interaction between genetic loading and early environmental stress.

(x) Further investigations of the consequences of childhood maltreatment should also be conducted, in particular using biological [e.g., neurotransmission, phenomena of neurotrophicity, neuroprotection, and neuroplasticity (99), or hypothalamic-pituitary-adrenal axis disruptions] and neuroimaging markers.

Once these issues have been dealt with, it should be possible to identify interactions between (probably nonspecific) childhood trauma and specific genetic susceptibility factors, leading to improvements in our understanding of the etiology of bipolar disorder and better prevention strategies. The identification of childhood trauma as a risk factor for bipolar disorder per se or for a more severe form of the disease may lead to potential trauma-focused preventive therapeutic interventions in at-risk populations. In other psychiatric disorders (e.g., in schizophrenia), tailored interventions to address the consequences of trauma have been shown to be clinically effective (100). All clinicians should be aware of such environmental risk factors and should routinely evaluate their patients’ histories for childhood trauma.

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Childhood trauma in bipolar disorder


