

Childhood Maltreatment and Psychopathology: A Case for Ecophenotypic Variants as Clinically and Neurobiologically Distinct Subtypes

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Objective: Childhood maltreatment increases risk for psychopathology. For some highly prevalent disorders (major depression, substance abuse, anxiety disorders, and posttraumatic stress disorder) a substantial subset of individuals have a history of maltreatment and a substantial subset do not. The authors examined the evidence to assess whether those with a history of maltreatment represent a clinically and biologically distinct subtype.

Method: The authors reviewed the literature on maltreatment as a risk factor for these disorders and on the clinical differences between individuals with and without a history of maltreatment who share the same diagnoses. Neurobiological findings in maltreated individuals were reviewed and compared with findings reported for these disorders.

Results: Maltreated individuals with depressive, anxiety, and substance use disorders have an earlier age at onset, greater symptom severity, more comorbidity, a greater risk for suicide, and poorer

treatment response than nonmaltreated individuals with the same diagnoses. Imaging findings associated with these disorders, such as reduced hippocampal volume and amygdala hyperreactivity, are more consistently observed in maltreated individuals and may represent a maltreatment-related risk factor. Maltreated individuals also differ from others as a result of epigenetic modifications and genetic polymorphisms that interact with experience to increase risk for psychopathology.

Conclusions: Phenotypic expression of psychopathology may be strongly influenced by exposure to maltreatment, leading to a constellation of ecophenotypes. While these ecophenotypes fit within conventional diagnostic boundaries, they likely represent distinct subtypes. Recognition of this distinction may be essential in determining the biological bases of these disorders. Treatment guidelines and algorithms may be enhanced if maltreated and nonmaltreated individuals with the same diagnostic labels are differentiated.

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Maltreated children are more likely to suffer psychiatric disorders over the course of their lifetime. In particular, they are more likely to develop major depression (1–5), bipolar disorder (6), anxiety disorders (2, 3, 7), posttraumatic stress disorder (PTSD) (2, 3), substance abuse (2, 8, 9), personality disorders (10, 11), and psychoses (12). Furthermore, it appears that survivors of early maltreatment differ in critical ways from other individuals with the same psychiatric diagnoses. Disorders emerge earlier in maltreated individuals, with greater severity, more comorbidity, and a less favorable response to treatment (13–15). Maltreated individuals may also have discernible brain abnormalities that are not present in their nonmaltreated counterparts (16, 17). Childhood maltreatment is also linked to a wide array of medical disorders, shortened life expectancy, and reduced telomere length (18, 19). Hence, an understanding of maltreatment as an etiological risk factor is crucial to the development of a science of preventive

psychiatry, to the design of effective therapeutic regimens, and to the delineation of an accurate nosology.

Our goal in this review is to advance the thesis (17, 20–23) that affected individuals with childhood maltreatment constitute a critically distinct subtype across depressive, anxiety, and substance use disorders. We also propose that the maltreated subtype may be thought of as a phenotypic specialization (phenocopy) resulting from environmental experience—or more precisely, an ecophenotype.

Why focus on maltreatment? It is maltreatment rather than exposure to other stressors, such as natural disasters, that consistently presents as the antecedent to psychopathology (24, 25). This makes sense. Children are dependent on the adults around them for their survival, and they can endure great hardship if they feel protected and cared for. But when the hardship is the product of their caretakers, and when it is the caretaker who must be protected against, it creates a stressor with far-reaching ramifications.

Epidemiology of Maltreatment Trauma

Maltreatment is characterized by sustained or repeated exposure to events that usually involve a betrayal of trust (20). Active examples include childhood sexual, physical, and various forms of emotional abuse. Passive examples include emotional and physical neglect. (See Figure 1 for proposed assessment criteria and definitions.) As might be expected, parents of maltreated children were often maltreated themselves and show high rates of untreated or undertreated psychopathology (26). Therefore, intergenerational transmission involves some combination of early life stress, deficient parenting skills, genetic or epigenetic risk, and family stressors (27).

Differences in definitions make it hard to draw firm conclusions about prevalence. However, retrospective and prospective studies suggest that exposure to one or more forms of childhood maltreatment range from 13.8% in 1-year prevalence rates to about 42% in retrospective estimates covering the full 18 years of childhood (28).

Supporting Methodology

Our conceptualization of ecophenotypes emerged from a systematic review of the English-language literature on the psychiatric and neurobiological consequences of childhood maltreatment. Details on how the review was conducted, as well as tabulated results of sexual abuse as a psychiatric risk factor, are presented in the data supplement that accompanies the online edition of this article. Studies selected for citation are representative. No contradictory studies showing a significant protective effect of maltreatment were encountered. In this review, we excluded disorders for which research suggests that the vast majority of patients were exposed to some type of abuse or neglect, such as borderline personality and dissociative identity disorder (10, 11, 29, 30). We also excluded schizophrenia and bipolar disorder, which are known to be highly heritable. Instead, we focused on moderately inheritable disorders for which major subsets of patients can be distinguished by positive or negative histories of childhood maltreatment. These disorders include major depression, anxiety disorders, posttraumatic stress disorder, and substance abuse. Childhood maltreatment or early adversity accounts for 30%–70% of the population attributable risk fraction for these disorders (1, 3, 9).

Maltreatment and Associated Psychopathology

Major Depressive Disorder

Some of the strongest evidence for an association between exposure to childhood maltreatment and the development of major depression can be found in the Adverse Childhood Experiences study (31), which showed that risk for depression increased in a graded, dose-dependent fashion with the

FIGURE 1. Childhood Maltreatment or Abuse Checklist

Before the age of 18 years: Sustained or repeated exposure to events involving a betrayal of trust by caretakers or other significant individuals in the child's life.

At least one of the following:

Active maltreatment

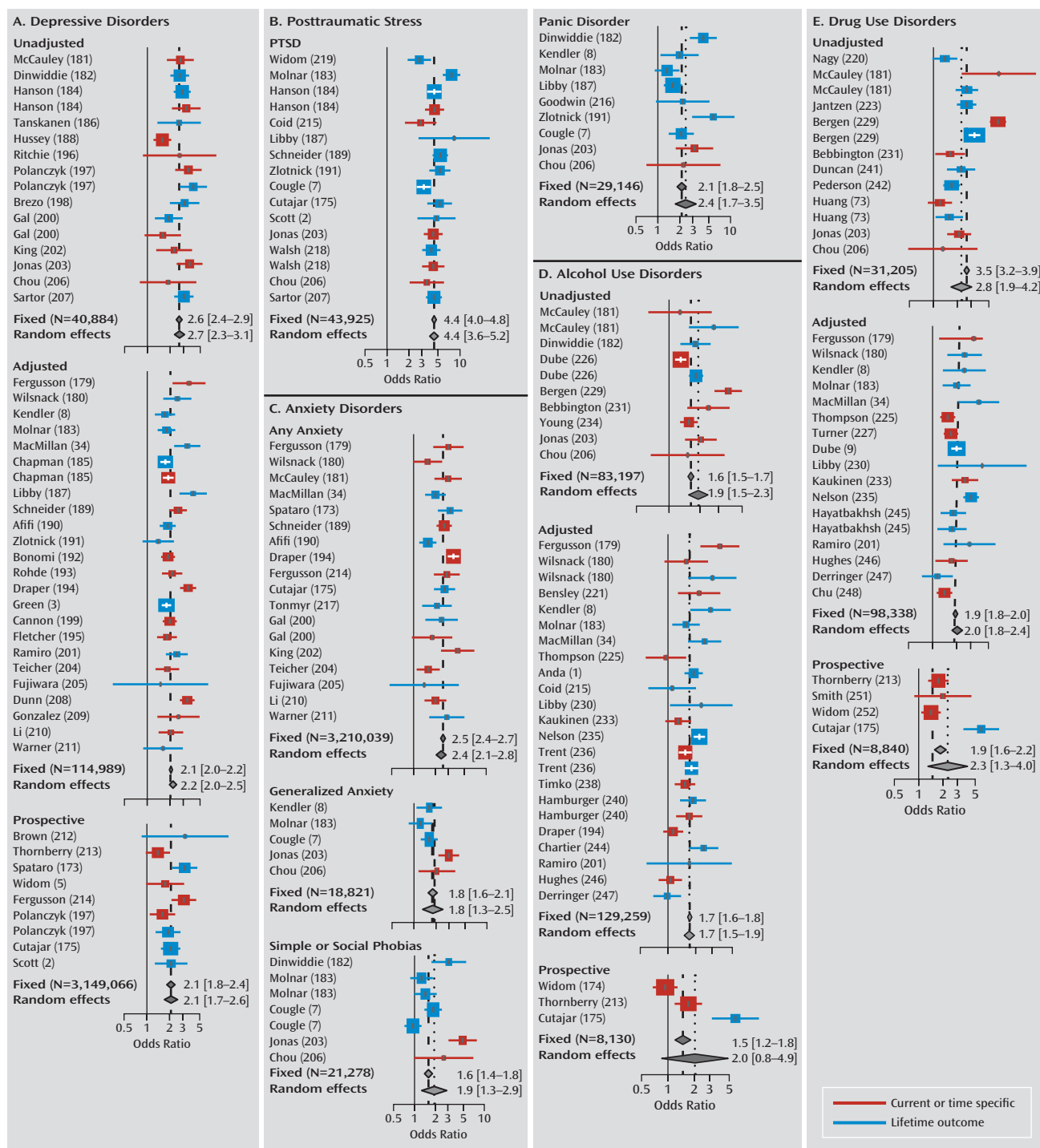
- _____ Emotional abuse
 - _____ Verbal aggression (communications intended to inflict intense humiliation, denigration, or extreme fear)
 - _____ Emotional manipulation (placing the child in a situation intended to elicit shame, guilt, or fear in order to serve the emotional needs of the perpetrator or to persuade the child to perform actions against his or her will or denigrating or destroying things of value to the child)
 - _____ Witnessing domestic violence (witnessing adults in the household intentionally humiliating, demeaning, or threatening to harm one another or other family members or actively engaged in physically harming family members by shoving, slapping, kicking, throwing objects, or using weapons against each other)
- _____ Physical abuse (hitting with objects, intentionally inflicting harm that results in bruises, welts, or the need for medical attention, shoving, kicking, dragging child by the hair, approaching the child with a weapon, forcing the child to remove clothing or otherwise humiliate him- or herself in front of others)
- _____ Extreme corporal punishment (discipline involving hitting with objects, intentionally inflicting harm that results in bruises, welts, or need for medical attention, forcing child to remove clothing or otherwise humiliate him- or herself in front of others ostensibly for discipline)
- _____ Sexual abuse (adults or older children touching or fondling the child's body in a sexual way or forcing the child to touch or fondle the perpetrator's body in a sexual way, or forcing the child to engage in other activities with a sexual content or attempted or actual sexual intercourse (oral, anal, or vaginal))

Passive maltreatment

- _____ Emotional neglect (failure to provide for the child's basic emotional needs, being emotionally unresponsive to the child's distress, not attending to the child's social and emotional development or not attending to the child's school performance, homework, etc., or expecting the child to routinely manage situations that are beyond his or her maturity level or are not safe)
- _____ Physical neglect (failure to provide for the child's basic needs, such as for food, clothing, physical safety, adequate supervision, dental health, and physical health)

number of maltreatment-related adverse childhood experiences. Exposure to one or more adverse childhood experiences accounted for 54% of the population attributable risk fraction for current episodes of depression (1) and 67% for suicide attempts (32). Having five or more adverse experiences increased the relative risk of receiving a prescription for an antidepressant 2.9-fold (6). Long-term prospective studies also indicate about a twofold greater risk attributable to maltreatment (2, 4, 5) (see Figure 2A). These findings are consistent with results of twin studies showing that heritability plays only a minor role in risk for moderate or even severe depressions (33).

Maltreatment increases the risk for depression in both males and females, although some studies suggest a greater

FIGURE 2. Forest Plots Showing Odds for Psychopathology in Individuals Exposed to Childhood Sexual Abuse or Multiple Forms of Maltreatment Including Sexual Abuse^a

^a References not included in the main text are provided in the online data supplement, along with further details of the analysis. The forest plots show odds ratios and 95% confidence intervals. Panels A–E address, respectively, diagnoses or suprathreshold symptoms of major depression; diagnoses of posttraumatic stress disorder; diagnoses or suprathreshold symptoms of anxiety disorders, including generalized anxiety disorder, panic disorder, and simple or social phobias; alcohol-related problems, including heavy episodic drinking, abuse, or dependence; and drug-related problems, including use of illicit drugs, abuse, or dependence. Studies were ordered within each cluster by year of publication. Multiple analyses within studies were pooled to provide assessment for overall risk across severity level and gender.

risk for depression in physically abused females than in physically abused males (34, 35). Hence, the greater female prevalence may be due, at least in part, to greater sensitivity to physical abuse and more frequent exposure to childhood sexual abuse (36).

Important clinical differences exist between depressive illnesses with and without childhood maltreatment. Depressions emerge earlier and have a more sustained course (13, 37) in maltreated individuals. These individuals also have more severe mood, neurovegetative, and endogenous symptoms and more comorbidities, particularly substance abuse (13, 22, 37, 38). Psychotic features are also more common, as are suicide attempts and deliberate self-harm (39).

Maltreated patients with depression also differ with respect to treatment response. A recent meta-analysis of depression outcome studies (13) confirmed that childhood maltreatment unequivocally predicts poor treatment outcome. However, it is also possible that maltreated patients with depression respond preferentially to therapies that are less effective for patients with depression who have no history of maltreatment. In a large clinical trial (40), chronically depressed participants received either pharmacotherapy with nefazodone, psychotherapy using the cognitive-behavioral analysis system of psychotherapy, or both treatments in combination. Psychotherapy was clearly superior to antidepressant monotherapy in the subset of participants with childhood trauma, and nefazodone provided little added benefit. In contrast, chronically depressed patients with no history of trauma or loss responded more favorably to nefazodone than to psychotherapy, and they benefited from combination treatment. On the other hand, in another study (41), maltreatment was associated with a poorer response to interpersonal therapy than to cognitive therapy or medication, and with rapid relapse. With hindsight, we can see that factors found over the years to predict treatment resistance in depression (i.e., early onset, comorbid anxiety and substance use disorders, axis II diagnoses, and presence of psychotic features) are the same factors now known to be characteristic of the maltreatment-related ecophenotype.

Neurobiological studies are beginning to provide compelling reasons for considering depression with a maltreatment history as a distinct subtype. Reduced hippocampal size is one of the more prominent neuroimaging findings in major depression. However, Vythilingam et al. (16) reported that reduced hippocampal size was present only in the subset of depressed individuals who had a history of maltreatment. On balance, there is now more consistent evidence for reduced hippocampal size in adults with a history of maltreatment than in adults with major depression. Furthermore, reduced hippocampal volume in maltreated individuals in the absence of depression or any psychiatric history has been observed in recent large-sample studies (42, 43). In short, what has been regarded as a key finding in major depression may instead be a consequence of early stress that serves in turn as a risk

factor. Indeed, reduced hippocampal volume can precede and partially mediate risk for depression with early stress (44).

Amygdala activation during exposure to sad or negative faces is another neuroimaging finding linked to major depression (45) that may be limited to depressed individuals with a history of maltreatment (24). Indeed, bilateral amygdala reactivity to emotional expression is enhanced by a history of emotional maltreatment whether or not the individual has depression (46).

Genetic and epigenetic risk factors may also be distinctly different in patients with major depression with and without a history of maltreatment. A comprehensive meta-analysis by Karg et al. (47) found strong support for a gene-by-environment interaction involving the serotonin transporter promoter polymorphism and risk for depression when the environmental experience was childhood maltreatment but only marginal support when the environmental experience involved postchildhood stressful events.

Epigenetic hypermethylation of the Nr3C1 gene results in decreased expression of glucocorticoid receptors and potential hypersecretion of cortisol during stress. Interestingly, Nr3C1 has been found to be hypermethylated in postmortem tissue from suicide victims with a history of maltreatment, but not in suicide victims without maltreatment or in nonsuicide comparison subjects (48).

While some have speculated that individuals without maltreatment who develop depression do so because of a dense family history and a high heritable risk, this supposition is not supported by our unpublished data or by the observation that less severe forms of depression show little evidence of heritability (33). However, nonmaltreated depressed individuals may show an array of noninherited rare copy number variants—short stretches of DNA that are deleted or duplicated between individuals that contribute disproportionately to risk (49).

Finally, depressed patients differ in their risk for autoimmune, metabolic, and cardiovascular disorders based on maltreatment history. This may be related to chronic low-grade inflammation. Longitudinal data show that depression and inflammation are strongly coupled in depressed individuals with maltreatment but not in those without maltreatment (4).

PTSD

Sexual abuse, physical abuse, and witnessing domestic violence are types of maltreatment that may fulfill the DSM-IV A1 criterion for a traumatic event (50), and they are major risk factors for the development of PTSD (Figure 2B). Scott et al. (2) reported an adjusted odds ratio of 4.86 for lifetime diagnosis of posttraumatic stress disorder in a prospective study of adults with a history of maltreatment. Furthermore, individuals who experienced both childhood adversity and adult traumatic events have been found to be more likely to develop PTSD than those who experienced either type of adverse event alone (51).

However, in recent years there has been growing concern about how well the DSM-IV conceptualization of posttraumatic stress, which is based on exposure to acute life-threatening events in soldiers, applies to maltreated children. Youngsters often experience traumatic or highly stressful events during a substantial portion of their life, which may be perpetrated by one or more family members rather than a faceless enemy. This has led to two important observations. First, DSM-IV criteria are not sufficiently developmentally sensitive. Severely maltreated children often do not meet full diagnostic criteria, as they frequently show symptoms in only two of three category clusters, but may be as impaired as children who meet full criteria (52). Furthermore, risk for posttraumatic stress in children appears to be influenced by frequency of exposure and multiplicity of exposure types rather than the degree to which they witnessed actual or threatened death or serious injury or experienced a threat to their physical integrity. Hence, children may be “traumatized” by repeated exposure to types of maltreatment that do not meet the A1 criterion for a traumatic event, such as emotional abuse (50).

Second, as van der Kolk (50) and others have articulated, traumatized children also show a complex array of problems, such as affective dysregulation, disturbed attachment patterns, behavioral regression, somatic symptoms, and altered attributions and expectancies that are not included in the current DSM conceptualizations and often lead to a host of comorbid diagnoses. Developmental trauma disorder has been proposed as a diagnostic category that more faithfully captures the critical events and clinical presentation of posttraumatic sequelae in chronically maltreated children (50).

However, developmental trauma disorder is best restricted to maltreated individuals with features of posttraumatic stress (see the online data supplement for further discussion). As noted above, many maltreated individuals are more accurately characterized as depressed, and timing of exposure may be a critical determinant. Schoedl et al. (53) found that individuals reporting sexual abuse after age 12 had a 10-fold greater risk of severe PTSD in adulthood than individuals reporting sexual abuse before age 12. Conversely, depressive symptoms were more severe in individuals reporting sexual abuse before age 12 than in those reporting it after age 12 (53).

Multiple lines of evidence suggest that maltreated individuals with PTSD continue to differ from their non-maltreated counterparts in adulthood. They show greater symptom complexity (54), more comorbid mood disorders (55), and more severe dissociation (56, 57) or alexithymia (58), leading to the designation “complex PTSD” (54, 59, 60). There may also be important neurobiological and genetic differences.

A key neuroimaging finding in PTSD, particularly in combat veterans (61), has been reduced hippocampal volume. However, a study of monozygotic twins discordant

for combat exposure found reduced hippocampal volume in combat-exposed individuals with posttraumatic stress as well as in their unexposed twins without posttraumatic stress (62). While these results may be confounded by individual drinking history or personality factors common to both twins, it is also possible that reduced hippocampal volume resulted from shared early stress and functioned as a risk factor for posttraumatic stress. As noted above, reduced hippocampal volume has been observed with considerable consistency in adults with a history of maltreatment. While some early studies with small sample sizes found reduced hippocampal size in maltreated adults with PTSD but not those without (63), recent studies with larger samples report reductions that are unrelated to posttraumatic stress (42, 43). Additional neuroimaging findings in PTSD, including amygdala hyperactivity and reduced medial prefrontal and anterior cingulate response (61), have also been observed in individuals with a history of childhood abuse, including those without PTSD or any psychopathology (43). Studies are clearly needed to ascertain the degree to which these neuroimaging findings are specific to PTSD, are specific to PTSD in the context of a history of maltreatment, or are a more general consequence of exposure to childhood maltreatment.

Similar to findings for depressive illness, a number of genetic polymorphisms appear to modulate risk for PTSD in individuals with a history of maltreatment. The most compelling involves polymorphisms of FKBP5, which regulates cortisol-binding affinity and the nuclear translocation of the glucocorticoid receptor (64, 65). Interestingly, Xie et al. (65) reported that among individuals with the TT genotype of rs9470080, those with no maltreatment history had the lowest risk for PTSD as adults, and those with a maltreatment history had the highest. This suggests that the search for genetic risk factors may be elusive if study subjects are not subtyped by maltreatment history.

Anxiety Disorders

The National Comorbidity Replication Study showed that childhood sexual or physical abuse was associated with a 2.03- to 3.83-fold increase in risk for specific phobias, social anxiety disorder, generalized anxiety disorder, and panic disorder with or without agoraphobia (7) (Figure 2C). Childhood adversity accounted for 32.4% of the population attributable risk fraction for anxiety disorders (3). Moreover, exposure to multiple types of childhood adversity increased the likelihood of receiving a prescription for an anxiolytic by twofold (6).

The impact of exposure to childhood maltreatment on the clinical presentation and treatment of anxiety disorders has been understudied. Patients with an anxiety disorder and a history of maltreatment have significantly higher rates of concurrent major depression (37, 66), more significant impairment in social functioning, higher state and trait anxiety scores (66), greater chronicity (37), greater symptom severity, and poorer quality of life (67). Severity

increases with the number of types of maltreatment experienced, and emotional abuse and neglect are especially salient risk factors for social anxiety disorder (67, 68). Lastly, in a clinical trial with paroxetine, social anxiety patients with a history of emotional abuse were the most likely to drop out of treatment (68).

Neuroimaging studies in individuals with anxiety disorders, particularly disorders involving intense fear and panic, such as panic disorder, specific phobias, and social anxiety, report evidence for amygdala hyperreactivity, which may stem from underactivity of the prefrontal cortex and insufficient inhibition of the amygdala (69, 70). Overactivation of the insula, a paralimbic region associated with perception of somatic sensations, has also been observed (70, 71). However, as indicated above, heightened amygdala activation has been observed in fMRI studies of adults without psychopathology if they were exposed to childhood maltreatment (43, 46). Moreover, a recent report (72) found that threatening faces produced overactivity in both the amygdala and the anterior insula in maltreated children with normal levels of anxiety. Hence, amygdala and insula findings are not specific to individuals with anxiety disorders. An alternative hypothesis is that enhanced amygdala and insula response to threat emerges as a consequence of exposure to childhood maltreatment and serves as a risk factor for the later development of anxiety disorders.

Substance Use Disorders

A substantial body of research shows the important role of maltreatment on risk for drug abuse and dependence (8, 9) (Figure 2D–E), although the nature of the association may be complicated by high rates of substance abuse in maltreating parents and by the possibility of prenatal exposure, prenatal malnutrition, and prematurity. A well-controlled epidemiological and co-twin study of women (8) found that nongenital childhood sexual abuse was associated with a 2.9-fold increase in risk for drug dependence and that sexual abuse involving intercourse was associated with a 5.7-fold increase. Risk was related to the number of different types of maltreatment an individual experienced. Compared with individuals with no adverse childhood events, adults with five or more adverse childhood events are seven to 10 times more likely to report illicit drug use problems, addiction to illicit drugs, and injection drug use (9). The population attributable risk fractions for these outcomes were 56%, 64%, and 67%, respectively (9). Results from the National Longitudinal Study of Adolescent Health and the National Youth Survey provide prospective evidence for a causal relationship between physical abuse and early adulthood substance abuse (73, 74).

A moderate number of studies have reported differences between substance-abusing individuals with and without a history of maltreatment. The maltreated ecophenotype is associated with an earlier age at initiation, a greater likelihood of engagement in risky sexual behaviors (75),

a greater risk for recent incarceration (76), greater ratings of psychological distress (77), and a greater risk for comorbid personality disorders (78). Physical maltreatment appears to be a particularly salient risk factor for the development of substance abuse (35) and progression to injection drug use (79).

Substance abusers with a history of maltreatment respond more poorly to treatment, with greater use of substances during treatment and more persistence of substance-related problems after discharge (80–82). Integrative therapies have been developed to address the combined impact of substance abuse and trauma-related psychopathology (83).

Key neuroimaging findings in substance abusers suggest the possibility of a “dopamine deficiency” that may manifest as reduced activation of the ventral striatum (nucleus accumbens) during rewarding or pleasurable tasks (84, 85). Furthermore, deficits in brain regions implicated in salience attribution (the orbitofrontal cortex) and inhibitory control (the anterior cingulate gyrus) may underlie the patterns of compulsive and impulsive behaviors that characterize addiction (86). Although these factors have not been well studied in maltreated individuals, the few relevant studies report reduced sensitivity to reward and decreased basal ganglia response (87), as well as structural and resting blood flow deficits in the ventral striatum, the anterior cingulate, and the orbitofrontal cortex (43, 88, 89). Further research is needed to ascertain whether these deficits are common to substance abusers in general or more specific to the subset with a history of childhood maltreatment.

How Does Maltreatment Increase the Likelihood of Developing So Many Different Psychiatric Disorders?

Could maltreatment be a nonspecific amplifying factor that “tips the balance” so that individuals at hereditary risk for one disorder or another become more likely to express it? In essence, then, could maltreatment act to enhance the “penetrance” of inherited genetic susceptibilities? This could provide an explanation for the elevations in both prevalence and associated comorbidities.

A richer and more compelling alternative is that the myriad possible outcomes of exposure to childhood maltreatment depend on the timing, type, and severity of exposure, plus a host of genetic factors that influence susceptibility and resilience, and an array of protective factors that attenuate risk. Epigenetic modifications in stress-response systems and neurotrophic factors regulating trajectories of brain development may be the driving force producing the various ecophenotypes. We believe that this explanation best accounts for the available data and suggest that psychiatric disorders presenting in individuals with a substantial history of childhood maltreatment be thought of as ecophenotypic variants or

TABLE 1. Childhood Maltreatment and Area or Integrity of the Corpus Callosum^a

First Author (Reference)	Types of Maltreatment	Diagnostic Requirement	Number of Subjects		Age (Years)		Gender	Medication	Main Corpus Callosum Findings ^b
			Exposed	Comparison	Mean	SD			
Teicher (90)	Sexual, physical, or neglect	Inpatients with versus without abuse	28	23	12.9	2.9	Both	No	Decrease in regions IV, III; males more affected than females
De Bellis (91)	Sexual, physical, or witnessing domestic violence	PTSD versus typical controls	44	61	12.1	2.3	Both	No	Decrease in regions IV, V–VII; males more affected than females
De Bellis (92)	Sexual, physical, or witnessing domestic violence	PTSD versus SES-matched controls	28	66	11.5	2.9	Both	No	Decrease in regions VII, IV–VI
De Bellis (144)	Sexual, physical, or witnessing domestic violence	PTSD versus SES-matched or typical controls	61	122	11.7	2.6	Both	No	Decrease in regions VII, I, VI; males more affected than females; reanalysis
Teicher (94)	Sexual, physical, or neglect	Inpatients with versus without abuse and controls	28	23 inpatients, 115 controls	12.2	3.4	Both	No	Decrease in regions IV, V–VII; males affected by neglect, females by sexual abuse; partial reanalysis
Zanetti (145)	Physical or sexual	BPD with versus without physical or sexual abuse and controls	10 (4 without physical or sexual abuse)	20 controls	29.1	9.1	Both	No	BPD versus controls NS; increase in regions V, VII in BPD with versus without abuse
Rusch (146)	Sexual	BPD with versus without sexual abuse and controls	20 (10 without physical or sexual abuse)	20 controls	27.6	6.8	Female	No	Decrease in region V in BPD versus controls; decrease in regions V, VI in BPD with versus without abuse
Kitayama (147)	Sexual, physical, or witnessing domestic violence	PTSD versus typical controls	9	9	37.3	9.4	Female	Yes	Decrease in region V and total area
Jackowski (95)	Sexual, physical, or witnessing domestic violence	PTSD versus typical controls	17	15	10.6	2.3	Both	No	Decreased FA in middle and posterior
Andersen (93)	Sexual	No diagnosis required; 27% with history of PTSD	26	17	19.8	1.4	Female	No	Decrease in region III; sensitive period, ages 9–10
Carrion (148)	Sexual, physical, or witnessing domestic violence	PTSD symptoms versus controls	24	24	11.0	2.2	Both	Yes	NS 8.7% decrease in region VII
Mehta (120)	Early deprivation, 24 months	Romanian orphans versus controls	14	11	16.1	0.8	Both	No	NS 6.5% decrease in absolute volume
Teicher (96)	Peer verbal abuse	No psychopathology	63	Used ratings, not groups	21.9	1.9	Both	No	Decreased FA in region VII; males and females affected to the same degree

continued

TABLE 1. Childhood Maltreatment and Area or Integrity of the Corpus Callosum^a (continued)

First Author (Reference)	Types of Maltreatment	Diagnostic Requirement	Number of Subjects		Age (Years)		Gender	Medication	Main Corpus Callosum Findings ^b
			Exposed	Comparison	Mean	SD			
Frodil (149)	CTQ score	Unaffected relatives with major depression, controls	6 relatives, 4 controls	15 relatives, 20 controls	36.3	12.9	Both	No	Decreased FA in region VII controls with versus without abuse; increase in FA in region VII, relatives with versus without abuse

^a References not cited in text are included in the online data supplement. Participants with borderline personality disorder without physical or sexual abuse were not considered to be unexposed to maltreatment given the likelihood that they experienced emotional abuse or neglect (11). BPD=borderline personality disorder; CTQ=Childhood Trauma Questionnaire; FA=fractional anisotropy (from diffusion tensor imaging); NS=not significant; PTSD=posttraumatic stress disorder; SES=socioeconomic status.

^b Statistically significant differences noted in one or more of the following regions: I=rostrum; II=genu; III=rostral body; IV=anterior midbody; V=posterior midbody; VI=isthmus; VII=splenium.

ecophenocopies (see the data supplement for strategies for capturing this in our nosology).

Neurobiological Correlates of Childhood Maltreatment

As indicated above, there is a growing body of reproducible findings linking childhood maltreatment to structural and functional brain differences. The most consistent finding is that of alterations in the corpus callosum, characterized by reduced midsagittal area (90–94) or decreased fractional anisotropy (diminished integrity) on diffusion tensor scanning (95, 96) (Table 1). Another reasonably consistent finding is reduction in hippocampal volume in adults (16, 93, 97–105) but not younger children (91, 92, 106, 107) with a history of maltreatment (Table 2). The hippocampus is likely the most stress-sensitive structure in the brain, and translational studies show that stress or glucocorticoids act on the hippocampus to suppress neurogenesis in the dentate gyrus and provoke remodeling of pyramidal cells in portions of the cornu ammonis, particularly CA3. A recent study (105) found that childhood maltreatment was associated with volume reductions in the same subfields in a relatively large population of young adults, suggesting that the same mechanisms may be at work.

There are also associations between exposure to early maltreatment and the attenuated structural or functional development of the neocortex (93, 108–113), including the anterior cingulate (109, 114–116), the orbitofrontal (89, 116, 117) and dorsolateral prefrontal cortex (88, 115), and the visual and auditory cortex (Table 3).

While maltreatment may be associated with alterations in the striatum/basal ganglia (87, 88, 114) and cerebellum (118, 119), most studies have not reported structural differences in the amygdala (91–93, 97, 102, 114). However, increased amygdala volume has been reported in children with institutional deprivation or rearing by chronically depressed mothers (120–122), while smaller amygdala volumes have been observed in adults with childhood

trauma and borderline personality disorder or dissociative identity disorder (100, 101, 103, 104). Nevertheless, there is good evidence of enhanced amygdala reactivity in maltreated individuals (17, 43, 46, 72).

Second, there appear to be sensitive periods when these regions are maximally susceptible to the effects of stress. Following this path of inquiry, our group examined the relationship between age at exposure to sexual abuse and observed alterations in brain morphology in a preliminary sample of young adult women (93). We found the hippocampus to be maximally susceptible to maltreatment in women exposed between the ages of 3 and 5 years. However, when maltreatment occurred at ages 9–10, the midportion of the corpus callosum was maximally susceptible, and at ages 14–16, the prefrontal cortex was affected. Thus, there appear to be specific windows of vulnerability in development that determine the negative effects of exposure. These observations are supported by translational research showing that synaptic density in the hippocampus but not the prefrontal cortex of rats is sensitive to the effects of early (preweaning) stress, while the opposite is true with regard to peripubertal stress (123, 124). Rao et al. (125) provided additional support for an early hippocampal sensitive period in humans, reporting that degree of parental nurturance at age 4, but not at age 8, predicted hippocampal volume at age 14.

Third, the effects of maltreatment on brain functioning may not appear immediately after exposure (124). Several studies have reported reductions in the gray matter volume of the hippocampus in adults with a history of maltreatment but not in maltreated children (Table 2). This pattern of results is consistent with translational studies showing that effects of early stress on the hippocampus first emerge during the transition between puberty and adulthood (124). The delay between exposure and neurobiological change may be particularly relevant, as a comparable time lag often occurs between exposure and emergence of depression or posttraumatic stress disorder (126).

TABLE 2. Childhood Maltreatment and Structure and Function of the Hippocampus^a

First Author (Reference)	Types of Maltreatment	Diagnostic Requirement	Number of Subjects		Age (Years)		Gender	Medication	Main Hippocampus Findings ^b
			Exposed	Comparison	Mean	SD			
Adults									
Bremner (97)	Physical or sexual	PTSD versus healthy controls	17	17	41.3	6.6	Female	Yes	L decreased 12%
Stein (99)	Sexual	PTSD or dissociative identity disorder versus SES-matched controls	21	21	31.1	6.4	Female	Yes	L decreased 5%
Driessen (103)	CTQ score	BPD versus healthy controls	21	21	29.6	6.5	Female	Yes	L, R decreased 16%
Vythilingam (16)	Physical or sexual	Major depression with versus without abuse and controls	21	11 major depression, 14 controls	31.4	6.9	Female	No	L decreased 15% in major depression with physical or sexual abuse versus control; NS for major depression without physical or sexual abuse versus control
Schmahl (104)	Physical or sexual	BPD with abuse versus comparison without BPD	10	23	30.3	8.0	Female	Yes	L decreased 11%, R 16%
Bremner (63)	Sexual	Abuse with PTSD, abuse without PTSD, and controls	10 with PTSD, 12 without PTSD	11	34.9	7.5	Female	No	L, R, decreased 19% for sexual abuse with PTSD versus control; NS for sexual abuse without PTSD versus control
Brambilla (102)	Physical or sexual	BPD versus healthy controls	10	20	33.0	8.9	Both	No	L, R decreased 6.8%, most marked in BPD with abuse
Pederson (150)	CTQ severe to extreme, pubertal	Abuse with PTSD, abuse without PTSD, controls	17 with PTSD, 17 without PTSD	17	25	6	Female	?	NS 2.8% decrease on L for abuse with PTSD versus control; NS 6.3% decrease on L for abuse without PTSD versus control
Vermetten (100)	Physical or sexual	Dissociative identity disorder with PTSD versus comparison	15	23	37.8	9.0	Female	Yes	L, R decreased 19.2%
Cohen (114)	ELSQ high versus low, 0–12 years	No psychopathology	122	84	39.9	17.2	Both	No	L, R decreased (p=0.07 and p=0.06)
Zetsche (151)	Physical or sexual	BPD with versus without physical or sexual abuse and controls	14 BPD with 11 BPD without physical or sexual abuse	25	26.7	6.7	Female	Yes	L decreased 5% (p=0.07), R decreased 6% (p=0.03) for BPD versus control; NS for BPD with versus without physical or sexual abuse
Andersen (93)	Sexual	No diagnosis required; 27% with history of PTSD	26	17	19.8	1.4	Female	No	Decreased 6.8% bilaterally; sensitive periods, ages 3–5, 11–13
Bonne (152)	Sexual, physical, emotional	PTSD with versus without abuse, controls	11	11 PTSD, 22 controls	35.9	10.4	Both	No	Decreased 9% bilaterally for PTSD versus control; NS for PTSD with versus without abuse
Weniger (153)	Physical or sexual	PTSD, dissociative disorders, and controls	10 PTSD 13 dissociative disorders	25	32.	7.1	Female	Yes	Decreased 18% bilaterally for PTSD versus control; NS for dissociative disorders versus control
Lenze (154)	CECA score	Remitted major depression with versus without abuse, controls	19	12 Remitted major depression, 24 controls	48.5	14.9	Female	Yes	Decreased L for remitted major depression versus control; abuse NS contribution

continued

TABLE 2. Childhood Maltreatment and Structure and Function of the Hippocampus^a (continued)

First Author (Reference)	Types of Maltreatment	Diagnostic Requirement	Number of Subjects		Age (Years)		Gender	Medication	Main Hippocampus Findings ^b
			Exposed	Comparison	Mean	SD			
Adults									
Soloff (155)	Physical or sexual	BPD with versus without physical or sexual abuse, controls	20 with 14 with-out physical or sexual abuse	30	26.6	7.9	Both	No	Decreased R, L for BPD versus control; NS for BPD with versus without physical or sexual abuse
Weniger (101)	Physical or sexual	BPD, controls	24	25	32.5	6.5	Female	Yes	Decreased 12% bilaterally (with or without comorbid PTSD)
Gatt (156)	ELSQ score	No psychopathology	89	Used ratings, not groups	36.2	12.7	Both	No	Decreased gray matter volume R, L with ELSQ ratings and MET polymorphism of BDNF
Frodl (98)	CTQ score	Major depression, healthy controls	43	42	44.1	12.4	Both	Yes	NS gray matter volume; emotional neglect: decreased white matter volume on L in females, L and R in males
Thomaes (157)	Physical or sexual	Complex PTSD, controls	33	30	35.5	11.0	Female	Yes	R decreased (p<0.04); R inverse correlation with abuse severity (p<0.02)
Landré (158)	Sexual	PTSD, unexposed controls	17	17	24.8	4.7	Female	No	NS
Sala (159)	Physical or sexual	BPD, matched controls	15 BPD (6 physical or sexual abuse)	15	33.5	7.9	Both	Yes	R decreased 12.7% for BPD versus control; R, L decreased for BPD with versus without physical or sexual abuse
Everaerd (160)	List of Threatening Life Events	No psychopathology; 5HTTLPR genotyping	357	Used ratings, not groups	23.7	5.6	Both	No	Gene-by-abuse-by-gender; decreased R, L for males with S'-allele and severe adversity (p<0.002)
Teicher (42)	CTQ and ACE scores	No diagnosis required; 46% exposed history major depression	104	89	21.9	2.1	Both	No	Decreased 6% in L subfields dentate gyrus and CA3; not related to major depression or PTSD
Dannlowski (43)	CTQ score	No psychopathology	148	Used ratings, not groups	33.8	10.4	Both	No	R decreased (p<0.05)
Carballedo (161)	CTQ score	No psychopathology, with versus without family of history major depression	20 positive, 20 negative family history	Used median split ratings	36.5	13.1	Both	No	Decreased L, R hippocampal heads in subjects with emotional abuse and positive family history
Children and adolescents									
De Bellis (91)	Sexual, physical, or witnessing domestic violence	PTSD versus typical controls	44	61	12.1	2.3	Both	No	NS 2.2% increase
Carrion (148)	Sexual, physical, or witnessing domestic violence	PTSD symptoms versus controls	24	24	11.0	2.2	Both	Yes	NS 7.6% decrease
De Bellis (162)	Sexual, physical, or witnessing domestic violence	PTSD versus typical controls	9	9	10.6	1.6	Both	Yes	NS at baseline or while followed longitudinally for >2 years
Chugani (163)	Early deprivation, mean 38 months	Romanian orphans versus epilepsy control	10	7	10.3	3.9	Both	No	Decreased PET glucose metabolism in L temporal region, including hippocampus

continued

TABLE 2. Childhood Maltreatment and Structure and Function of the Hippocampus^a (continued)

First Author (Reference)	Types of Maltreatment	Diagnostic Requirement	Number of Subjects		Age (Years)		Gender	Medication	Main Hippocampus Findings ^b
			Exposed	Comparison	Mean	SD			
Children and adolescents									
De Bellis (92)	Sexual, physical, or witnessing domestic violence	PTSD versus SES-matched controls	28	66	11.5	2.9	Both	No	NS 1.8% decrease
Tupler (107)	Sexual, physical, or witnessing domestic violence	PTSD versus SES-matched or typical controls	61	122	11.7	2.6	Both	No	NS gray matter volume; increased white matter volume; reanalysis
Carrion (106)	Sexual, physical, or witnessing domestic violence	PTSD symptoms	15	0	10.4	8–14	Both	Yes	Inverse correlation (r=−0.48) between volume and cortisol level over 12–18 months
Mehta (120)	Early deprivation, 24 months	Romanian orphans versus controls	14	11	16.1	0.8	Both	No	L, R decreased 16% absolute, NS after adjusted for brain volume
Rao (44)	Early life adversity	Major depression, high risk, and controls	30 major depression 22 high risk, 35 controls	Ratings of exposure within each group	14.9	1.8	Both	No	Decreased R, L with early life adversity in high risk and controls; hippocampal volume partially mediated risk for major depression with early life adversity
Carrion (164)	Sexual, physical, or witnessing domestic violence	PTSD symptoms versus controls	16	11	13.9	2.0	Both	Yes	Abnormal (decreased) R BOLD response on verbal memory task
Maheu (165)	Caregiver deprivation—emotional neglect	Orphans or foster care versus controls	11	19	13.5	2.6	Both	No	Abnormal (increased) L BOLD response to fearful and angry versus neutral faces
Tottenham (121)	Early deprivation, 63 months	Orphans versus healthy controls	34	28	8.9	2.1	Both	?	NS 2.5% decrease on L in late adoptees (after 15 months)
Edmiston (166)	CTQ score	No psychopathology	42	Used ratings, not groups	15.33	1.37	Both	No	Decreased with total scores on R, L in females; decreased with emotional neglect on R, L in males and females
Lupien (122)	Mothers with chronic major depression	Exposed versus controls	17	21	10		Both	No	NS

^a References not cited in text are included in the online data supplement. Participants with borderline personality disorder without physical or sexual abuse were not considered to be unexposed to maltreatment given the likelihood that they experienced emotional abuse or neglect (11). 5HTTLPR=serotonin transporter promoter polymorphism; BDNF=brain-derived neurotrophic factor; BOLD=blood-oxygen-level-dependent; BPD=borderline personality disorder; CECA=Childhood Experience of Care and Abuse; CTQ=Childhood Trauma Questionnaire; ELAQ=Early Life Stress Questionnaire; L=left; NS=nonsignificant; PET=positron emission tomography; PTSD=posttraumatic stress disorder; R=right; SES=socioeconomic status.

^b Statistically significant differences (percent reduction) observed in right or left hippocampal volume, gray matter volume, white matter volume, or function. In most studies measures of hippocampal volume were adjusted for differences in total brain volume.

TABLE 3. Childhood Maltreatment and Structure and Function of the Cerebral Cortex^a

First Author (Reference)	Types of Maltreatment	Diagnostic Requirement	Number of Subjects		Age (Years)		Gender	Medication	Main Cortical Findings ^b
			Exposed	Comparison	Mean	SD			
De Bellis (91)	Sexual, physical, or witnessing domestic violence	PTSD versus typical controls	44	61	12.1	2.3	Both	No	Increased prefrontal cerebrospinal fluid (volume loss)
De Bellis (109)	Sexual, physical, or witnessing domestic violence	PTSD versus typical controls	11	11	10.2	2.9	Both	No	Decreased N-acetyl aspartate/creatinine ratio in anterior cingulate
Carrión (108)	Sexual, physical, or witnessing domestic violence	PTSD symptoms versus controls	24	24	11.0	2.2	Both	Yes	Decreased frontal asymmetry
Chugani (163)	Early deprivation, mean=38 months	Romanian orphans versus epilepsy control	10	7	10.3	3.9	Both	No	Decreased PET glucose metabolism in R, L orbital frontal gyrus, infralimbic prefrontal cortex
De Bellis (92)	Sexual, physical, or witnessing domestic violence	PTSD versus SES-matched controls	28	66	11.5	2.9	Both	No	Increased prefrontal cerebrospinal fluid (volume loss)
De Bellis (167)	Sexual, physical, or witnessing domestic violence	PTSD versus typical controls	43	61	12.1	2.3	Both	No	Increased R, L superior temporal gyrus gray matter volume; reanalysis
De Bellis (144)	Sexual, physical, or witnessing domestic violence	PTSD versus SES-matched or typical controls	61	122	11.7	2.6	Both	No	Increased prefrontal cerebrospinal fluid (volume loss); reanalysis
Brambilla (102)	Physical or sexual	BPD versus healthy controls	10	20	33.0	8.9	Both	No	NS in temporal lobes and dorsolateral prefrontal cortex
Richert (168)	Sexual, physical, or witnessing domestic violence	PTSD symptoms versus controls	23	24	11.0	2.2	Both	Yes	Increased middle inferior ventral prefrontal gray matter volume; reanalysis (108)
Cohen (114)	ELSQ high versus low, 0–12 years	No psychopathology	122	84	39.9	17.2	Both	No	Decreased anterior cingulate total volume
Kitayama (169)	Physical, sexual	PTSD versus healthy controls	8	13	39.3	8.2	Both	?	Decreased R anterior cingulate volume
Andersen (93)	Sexual versus healthy controls	No diagnosis required; 27% with history of PTSD	26	17	19.8	1.4	Female	No	Decreased total frontal gray matter volume; sensitive period, ages 14–16
Tomoda (111)	Sexual versus healthy controls	No diagnosis required; most without axis I, II disorders	23	14	19.7	1.4	Female	No	Decreased occipital gray matter volume in BA 17–18; sensitive period, before age 12; partial reanalysis (93)

continued

TABLE 3. Childhood Maltreatment and Structure and Function of the Cerebral Cortex^a (*continued*)

First Author (Reference)	Types of Maltreatment	Diagnostic Requirement	Number of Subjects		Age (Years)		Gender	Medication	Main Cortical Findings ^b
			Exposed	Comparison	Mean	SD			
Tomoda (115)	Harsh corporal punishment versus healthy controls	No diagnosis required; most without axis I, II disorders	23	22	21.7	2.0	Both	No	Decreased gray matter volume in dorsolateral, anterior cingulate, and medial prefrontal
Carrion (148)	Sexual, physical, or witnessing domestic violence	PTSD symptoms versus controls	24	24	11.0	2.2	Both	Yes	Increased R, L inferior and superior prefrontal gray matter volume; reanalysis (108)
Carrion (170)	Sexual, physical, or witnessing domestic violence	PTSD symptoms versus controls	30	15	13.2	2.1	Both	No	Decreased L ventral and inferior prefrontal gray matter volume; inverse correlation between prebedtime cortisol level and L ventral gray matter volume
van Harmelen (171)	Emotional abuse or neglect	Major depression or anxiety disorders versus controls	84	97	37.5	10.4	Both	Yes	Decreased L dorsomedial prefrontal gray matter volume, independent of psychopathology
Sheu (88)	Harsh corporal punishment versus controls	No diagnosis required; 63% no lifetime history	19	23	21.9	2.1	Both	No	Increased T ₂ relaxation time (decreased regional cerebral blood volume) in R, L dorsolateral prefrontal
Hanson (89)	Physical versus healthy controls	No diagnosis required	31	41	11.8	1.1	Both	Yes	Decreased R orbital frontal, dorsolateral, temporal, and left and right parietal lobes
Frodl (98)	CTQ score	Major depression and healthy controls	43	42	44.1	12.4	Both	Yes	Physical neglect: decreased prefrontal gray matter volume
Thomaes (157)	Physical or sexual	Complex PTSD and controls	33	30	35.5	11.0	Female	Yes	Decreased R dorsal anterior cingulate, R orbitofrontal
Landré (158)	Sexual	PTSD and unexposed controls	17	17	24.8	4.7	Female	No	NS regional measures of cortical thickness
Tomoda (112)	Parental verbal abuse versus healthy controls	No diagnosis required, 48% with history of mood disorder	21	19	21.2	2.2	Both	No	Increased L superior temporal gyrus gray matter volume
Edmiston (166)	CTQ score	No psychopathology	42	Used ratings not groups	15.33	1.37	Both	No	Decreased dorsolateral, orbitofrontal, subgenual prefrontal gray matter volume

continued

TABLE 3. Childhood Maltreatment and Structure and Function of the Cerebral Cortex^a (continued)

First Author (Reference)	Types of Maltreatment	Diagnostic Requirement	Number of Subjects		Age (Years)		Gender	Medication	Main Cortical Findings ^b
			Exposed	Comparison	Mean	SD			
Gerritsen (172)	List of Threatening Life Events	No psychopathology; BDNF polymorphism	568	Used ratings not groups	23.4	5.4	Both	No	Decreased anterior cingulate and medial orbitofrontal at 1.5-T but not 3-T; G×E BDNF versus events for subgenual anterior cingulate
Carballedo (161)	CTQ score	No psychopathology, with versus without family history of major depression	20 positive 20 negative family history	Used median split ratings	36.5	13.1	Both	No	Decreased L dorsolateral and medial prefrontal, R anterior cingulate with emotional abuse and positive family history
Tomoda (128)	Witnessed domestic violence versus healthy controls	No diagnosis required, 59% past psychiatric history	22	30	21.7	2.2	Both	No	Decreased gray matter volume and thickness in R lingual gyrus (BA 18), decreased thickness R, L V2 and L occipital pole; sensitive period, ages 11– 13

^a References not cited in text are included in the online data supplement. Participants with borderline personality disorder without physical or sexual abuse were not considered to be unexposed to maltreatment given the likelihood that they experienced emotional abuse or neglect (11). 5HTTLPR=serotonin transporter promoter polymorphism; BA=Brodman's area; BDNF=brain-derived neurotrophic factor; BPD=borderline personality disorder; CTQ=Childhood Trauma Questionnaire; ELSQ=Early Life Stress Questionnaire; G×E=gene-by-environment interaction; L=left; NS=nonsignificant; PET=positron emission tomography; PTSD=posttraumatic stress disorder; R=right; SES=socioeconomic status.

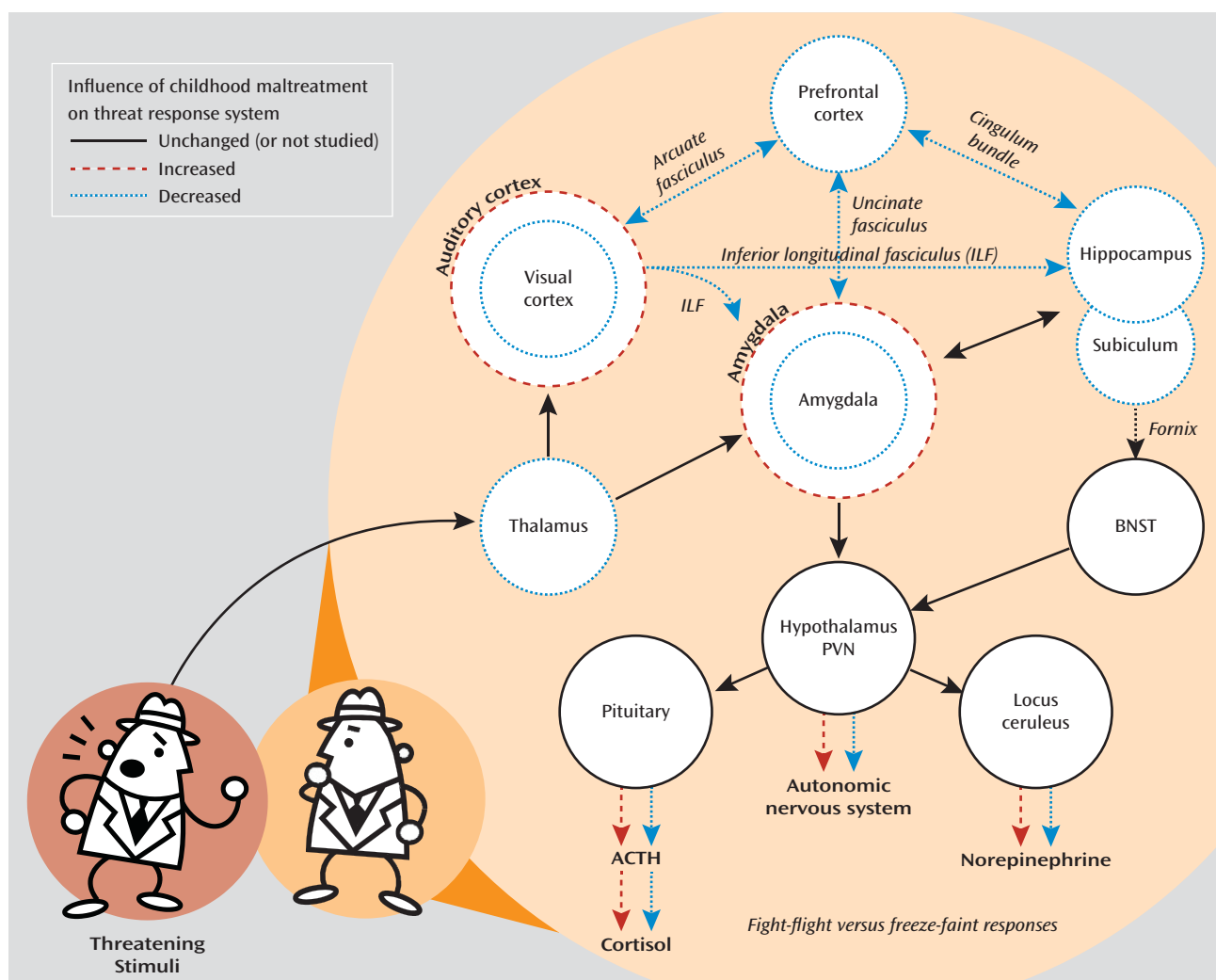
^b Statistically significant differences observed in right or left regional cortical volume, gray matter volume, white matter volume, thickness or function. In most studies, measures of cortical volume were adjusted for differences in total brain volume.

Fourth, maltreatment also appears to affect the development of sensory systems and pathways that process and convey the adverse experience. For example, parental verbal abuse is associated with decreased fractional anisotropy in the arcuate fasciculus, which interconnects Wernicke's and Broca's areas (127), and with alterations in gray matter volume in the auditory cortex (112). Conversely, witnessing domestic violence is associated with a reduction in gray matter volume in the primary and secondary visual cortex (128) and with decreased fractional anisotropy in the inferior longitudinal fasciculus, which interconnects the visual cortex and the limbic system to shape our emotional and memory response to things that we see (129).

Figure 3 places these findings in context by showing that many of the identified neuroanatomical abnormalities are interconnected and are components of a circuit regulating response to potentially threatening stimuli. Briefly, the thalamus and sensory cortex process threatening sights and sounds and convey this information to the amygdala (130). Prefrontal regions, particularly the ventromedial and orbitofrontal cortex, modulate amygdala response, perhaps turning it down with the realization that something is not

actually a threat or, in other cases, irrationally amplifying it (130). The hippocampus also processes this information and plays a key role in retrieving relevant explicit memories (130). The amygdala integrates this information and signals the paraventricular nucleus of the hypothalamus, which in turn regulates autonomic (e.g., heart rate) and pituitary-adrenal hormonal responses and signals the locus ceruleus, which regulates the intracerebral noradrenergic response. The hippocampus, through the subiculum and bed nucleus of the stria terminalis, also modulates paraventricular response, particularly to psychological stressors (131).

Hence, childhood maltreatment, by affecting the development of key components of this system, reprograms response to subsequent stressors. The influence of maltreatment on autonomic and hypothalamic-pituitary-adrenal response to psychological stressors has been evaluated in a series of studies using the Trier Social Stress Test. Heim et al. (132) first reported that women with a history of physical or sexual abuse had *heightened* cortisol, ACTH, and heart rate response to stress challenge. Subsequent studies have generally painted a different picture, with evidence emerging for a *blunting* of cortisol

FIGURE 3. Neurocircuit Regulating Stress Response to Threatening or Salient Stimuli^a

^a Childhood maltreatment alters development of regions and pathways within this circuit, which serves to reprogram response to subsequent stressors, resulting in either exaggerated or blunted responses. Based primarily on LeDoux (130). ACTH=adrenocorticotrophic hormone; BNST=bed nucleus of stria terminalis; PVN=paraventricular nucleus of hypothalamus.

response in adults with a history of maltreatment (133–136). Nevertheless, some individuals show an augmented response, consistent with an enhanced fight-or-flight reaction, and others show a blunted response, consistent with freezing. This divergent pattern of response may be influenced by the type (137) and timing (138) of maltreatment.

Psychosocial Correlates of Exposure

Simultaneous to disruptions in brain development that occur with exposure to mistreatment are alterations in the development of psychological structures. Alterations have been observed in the form of poor self-concept, feelings of worthlessness, and negative views of the world. Furthermore, victims of maltreatment show deficits in what is called deontic reasoning (reasoning about duties and obligations we owe one another), which puts victims at increased risk for future victimization (139). Victims of maltreatment are also more likely to show insecure

attachment, associated with diminished expectations of support as well as poor emotion regulation capacities (140).

Treatment Implications

The first question is whether interventions exist that can reduce a child's risk of abuse and neglect. The Nurse-Family Partnership has been shown in randomized controlled trials to reduce the incidence of abuse (particularly physical abuse) and neglect of first-born children of high-risk mothers (141). There is also emerging evidence for the efficacy of other interventions against the emergence or reoccurrence of physical abuse. However, no interventions have been shown to be effective in reducing risk for sexual abuse, emotional abuse, witnessing domestic violence, or recurrence of neglect (141).

The second question is whether preemptive interventions exist that can reduce long-term risk for psychiatric

illness in maltreated children prior to the emergence of psychopathology. This is an important but largely unexplored area. Third, are there good acute treatments with long-term benefits for maltreated children with psychopathology? Trauma-focused cognitive-behavioral therapy for sexually abused children with symptoms of posttraumatic stress has the most evidence of efficacy (141), but long-term outcome studies are sparse. Assessing and treating parents may also be critical, as maltreatment is often associated with parental psychopathology and parenting problems (26). Recent efforts to develop neurobiologically informed treatments provide preliminary evidence that lower post-treatment cortisol levels may be associated with reduced effects on hippocampal development (106).

Finally, what can be recommended for adults with ecophenotypic variants of major depression, anxiety disorders, substance abuse, or posttraumatic stress? Results of a recent meta-analysis show that depressed individuals with a history of maltreatment respond more poorly to treatment (13), suggesting that standard first-line recommendations for depression may be inadequate for these individuals. The finding that the cognitive-behavioral analysis system of psychotherapy was more effective than nefazodone in maltreated individuals with chronic depression (40) is intriguing, but research is needed to ascertain whether these findings apply to other medications, to other systems of therapy, and to maltreated individuals with less chronic conditions. Integrative trauma-focused treatments have been developed for maltreated individuals with substance abuse that are more helpful than standard treatments, although the results have been far from ideal (83). Childhood maltreatment is often associated with development of insecure attachment patterns (24), and mentalization-based therapy appears to have beneficial effects in patients with insecure attachment patterns across a range of disorders, including major depression, substance abuse, and borderline personality disorder (142). Efforts to reduce allostatic load and inflammation (19) may also be of benefit for maltreated individuals.

Recent recommendations for adults with maltreatment-related posttraumatic stress are to adopt a sequential approach that begins with safety, education, stabilization, skill building, and development of the therapeutic alliance before endeavoring to revisit or rework the trauma, as this may be destabilizing (143). Overall, we suspect that unknowingly mixing maltreated and nonmaltreated subtypes in treatment trials may have left us with an incomplete understanding of risks and benefits. Stratifying study subjects by maltreatment history may provide more definitive insights and delineate a clearer course of action for each subtype.

Conclusions

Childhood maltreatment is a complex etiological agent that appears to vary in impact according to the timing,

type, and severity of exposure, coupled with a number of susceptibility and resilience cofactors. We propose using the term *ecophenotype* to delineate these psychiatric conditions. We specifically recommend, as a first step, adding the specifier “with maltreatment history” or “with early life stress” to the disorders discussed here so that these populations can be studied separately or stratified within samples. This will lead to a richer understanding of differences in clinical presentation, genetic underpinnings, biological correlates, treatment response, and outcomes. Doing so may also help resolve inconsistencies in the literature resulting from unassessed differences in the percentage of maltreated subjects within a given study.

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Dr. Teicher has developed and patented technology for the assessment of attention deficit hyperactivity disorder, which has been licensed by McLean Hospital to BioBehavioral Diagnostic Company (BioBDx), and he has received research support from CNS Response and the Litebook Company. Dr. Teicher has received royalty payments, research support, travel reimbursement, and consulting fees from BioBDx.

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