CHILDHOOD MALTREATMENT AND NEUROBIOLOGICAL VULNERABILITY TO DEPRESSION: A REVIEW

Lorenzo Bassani, Niki Antypa, Alessandro Serretti

Abstract

Numerous studies suggest that child abuse and neglect significantly increase risk for depression. Major depressive disorder (MDD) is a highly recurrent disorder. This high rate of recurrence of depressive episodes probably reflects the presence of stable vulnerability factors: among the strongest risk factors for developing MDD are experiences of childhood maltreatment. Every year in the U.S. over 500,000 cases of physical and sexual abuse are documented. Despite the widely appreciated magnitude of the problem, the precise mechanism by which childhood trauma may increase the risk for depression remains unclear.

Research comparing depressed individuals with and without a history of early life trauma suggests important differences on several key neurobiological features including endocrine and autonomic activity, as well as on region-specific brain morphology. This evidence suggests that brain morphology and physiology are influenced by both heritable and stress-induced influences, which have been observed in both human and animal models. In this context, cognitive models of depression propose that biased processing of emotional material is a stable vulnerability factor that affects the onset, maintenance, and recurrence of depressive episodes. Cognitive biases can be observed in depressed and abused participants: these impairments may underlie reduced affect regulation and social interaction, and therefore contribute to the development and maintenance of such disorder.

Key words: childhood maltreament, depression, vulnerability, emotional processing

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Introduction

Child maltreatment, was «discovered» as a social problem in Western industrialized countries in the 1870s. The physical violence, starvation and neglect of 9-year-old Mary Ellen in the United States (U.S.) in 1874 precipitated the development of the world's first organization against child cruelty, the *New York Society for the Prevention of Cruelty to Children* (Radford et al. 2011).

A clear operational definition of child maltreatment is fundamental to effective preventive strategies. The legal definitions related to child maltreatment vary from one country to the next. Child maltreatment can be defined as «*all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power*» (Butchart et al. 2006). Definitions and prevalence of different types of abuse are reported in Table 1. Within child protection practice, child maltreatment is conventionally defined as severe when physical and emotional abuse, neglect and contact sexual abuse by any adults, parents, guardians or peer are substantiated. Experiences of maltreatment can be defined as severe on the basis of the type of maltreatment, its frequency and accumulative pattern, the psychological impact and the victim's perception. Physical harm is one indicator of severity, but child maltreatment does not always result in injuries: there may be no physical injuries in very harmful cases of child sexual or emotional abuse. The frequency and accumulative pattern of the behavior may be very harmful, creating psychological distress. Typically child abuse and neglect are not discrete events but a pattern of behavior, a process of undermining and debilitating the child's wellbeing and healthy development. Victims

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of abuse often report the psychological impact as being more damaging than the physical injuries. Measuring the psychological impact is difficult because we do not know whether the poorer emotional wellbeing was a contributory factor to or an outcome of the abuse. Victim perception can be an indicator of severity of impact but within a power or dependency relationship, it can be difficult for the child to name the experience as being abuse or neglect.

By all standards of measurements, the problem of child maltreatment is enormous in terms of both its cost to the individual, and its cost to society. The true prevalence of child maltreatment anywhere in the world is a matter of speculation. Reliable measurement of the frequency and severity of child maltreatment is complex and difficult to achieve. It has always proved difficult to obtain accurate figures for child maltreatment incidence and prevalence because of variations in methods of ascertainment and recording. Even if child maltreatment is a global problem with serious life-long consequences, there are no reliable global estimates for the prevalence of child maltreatment. Data for many countries, especially low- and middle-income countries, are lacking. While some of the variations might reflect different experiences that children have in different countries, there are conceptual and methodological differences that exist in the child abuse research that also give rise to these differences. Current estimates vary widely depending on the country and the method of research used (see table 1). Estimates depend on the definitions of child maltreatment used, the type of child maltreatment studied, the coverage and quality of official statistics and the coverage and quality of surveys that request self-reports from victims, parents or caregivers. The research studies vary in (Gilbert et al. 2009, Hamby et al. 2000):

- The sources used to produce information on the prevalence of child abuse and neglect. Three types of studies that measure the frequency of maltreatment can be used: community studies based on self-reports from victims who are old enough to comply with surveys, studies based on parents reporting severe physical punishment or patterns of care, and official statistics from agencies investigating victims (child-protection services) or police (investigating victims and offenders).
- The recruitment of participants. Most of the studies recruit large samples of participants randomly from the wider population. There are many studies which use clinical or service user samples or convenience samples such as university students or self-selecting volunteers. The prevalence estimates tend to be lower for research based on samples drawn at random from general populations than those based on research with less representative volunteer or service user samples.
- The definitions used to assess the prevalence of abuse and neglect. Some studies consider only one form of abuse, such as physical violence, sexual abuse or peer abuse. Others consider a broader range of maltreatment, including physical violence, sexual abuse, emotional abuse, neglect and exposure to domestic violence.
- The measures used to assess the prevalence of abuse and neglect, which can radically influence the results. Validated measures ask young people direct and specific questions about particular acts, using questions tested for internal consistency and pre-test reliability. Age-appropriate questions that give behavioral descriptions of events help respondents to think about specific incidents and are preferred over questions that use legal terminology or ask respondents to label themselves as experiencing abuse.

All these measures have biases and inconsistencies. Despite the uncertainty of these estimates, the gap between the low rates of maltreatment substantiated by child-protection agencies and the ten-fold higher rates reported by victims or parents underlines the fact that only a few children who are maltreated receive official attention (Finkelhor, 2008). Anyhow, it is clear that child maltreatment of all kinds is common across cultures, social and economic groups, and in both genders. Substantial variation between studies and across time probably reflect ascertainment and reporting difficulties, but nonetheless it is clear that official rates of reported child abuse represent the tip of the iceberg of maltreatment experienced by children across cultures.

Negative experiences in childhood increases the risk of developing a psychopathology across the lifespan, as proposed in the past by different theorists (Beck 1967, Bowlby 1973 and 1980). A large study provided evidence for a strong dose–response relationship between childhood adversities (sexual abuse, physical abuse, witnessing paternal violence) and general mental health problems in adulthood (Edwards et al. 2003). Although some theorists have suggested that childhood abuse would be a nonspecific risk factor for psychopathology in adulthood, others have hypothesized that definite forms of childhood abuse may contribute specific vulnerability to different types of psychopathology (Cicchetti et al. 2000). Despite the difficulties with defining and studying maltreatment, researchers have begun to investigate the impact of its different components on psychological alteration. There is evidence that different forms of maltreatment may be uniquely related to certain types of psychological difficulties. In particular, childhood maltreatment has been consistently associated with an increased risk for suffering from major depression in adulthood. The aim of this review was therefore to investigate and characterize the relationship between childhood maltreatment and depression, as well as discuss the potential neurobiological mechanisms through which the two phenomena may be linked.

Method

For identifying relevant literature for the present review we searched Pubmed and Medline for published articles until January 2013. The main search terms used were: “child* maltreatment”, “child* abuse”, “neurobiolog*”, “stress”, “cognit*” “depress*” in different combinations. After an initial search, references were reduced to comprehensive reviews and individual articles not included in reviews.

First, we discuss the association between childhood maltreatment and major depression (also in relation to other types of psychopathology), as well as the impact of different types of childhood maltreatment on adult depression. Second we examine neurobiological correlates of depression in maltreated samples. The main inclusion criterion for this second part was that studies needed to have assessed at least one type of childhood maltreatment in relation to some neurobiological and/or cognitive system implicated in the pathophysiology of depression. Reviews explaining the neurobiology of depression were also included in order to provide a more comprehensive overview and understanding of the pathophysiology involved in this disorder, and

subsequently address the effects of maltreatment on the implicated systems. The full text of studies was retrieved and only published studies in the English langaguage were included.

Childhood maltreatment and Major Depression

Several studies have provided undeniable evidence for a strong association between various forms of early life stress and increased risk for depression (Kessler et al. 1993, Fergusson et al. 1996, Kessler et al. 1997, Felitti et al. 1998, Kendler et al. 2000, Kendler et al. 2002, Kendler et al. 2006, Jaffee et al. 2002, Nelson et al. 2002, Dube et al. 2003, Maercker et al. 2004). Felitti et al. reported 4-fold increases in the risk of depression in individuals with multiple childhood adverse experiences (Felitti et al. 1998). In the same population, a dose–response relationship between the severity of experienced childhood adversities and the presence of a depressive episode in the past year or lifetime chronic depression was reported (Chapman et al. 2004). Furthermore, the experience of any childhood adversity increased the risk of attempted suicide in childhood, adolescence or adulthood 2- to 5-fold (Dube et al. 2001). Early life stress events also increase the risk for an early age of onset of depression (Widom et al. 2007).

Numerous studies show a close relationship between childhood sexual and physical abuse and depression in adult life. On the other hand, there are few studies that have examined the psychobiological consequences of neglect and emotional abuse (Widom et al. 2007). One study has examined the relative specificity of childhood emotional, physical, and sexual abuse to diagnoses of depression versus other disorders in adulthood: adult psychiatric outpatients' reports of childhood emotional abuse were more strongly related to the presence of current depressive disorders than anxiety disorders. In contrast, reports of childhood physical and sexual abuse were equally strongly related to both depressive and anxiety disorders (Gibb et al. 2003). Hovens et al. (2010; 2012) reported that childhood trauma rather than childhood life events appears to be an important risk factor for depressive and anxiety disorders in adulthood, in particularly in cases of comorbid depression and anxiety. In contrast, the childhood life event index did not show any significant relationship with psychopathology. A reported history of childhood trauma is associated with a higher risk of anxiety and depressive disorders in adulthood and with an increasing order from anxiety to depressive to comorbid anxiety and depressive disorders. Childhood trauma, but not childhood life events, is associated with an increased persistence of both comorbidity and chronicity in the course of anxiety and / or depressive disorders. The impact of childhood trauma appears to be greater in depressive than in anxiety disorders (Hovens et al. 2010, Hovens et al. 2012). It should also be noted that most maltreated children experience more than one form of abuse and/or neglect (literature refers to it as Child Multi-type Maltreatment - CMM) (Higgins and McCabe 2001).

Specific types of childhood maltreatment and major depression

It is well documented that Childhood Sexual Abuse (CSA) has long-term effects that increase the risk for developing psychopathology, and depression in particular. Studies of community college, and clinical groups of women demonstrate a clear relationship between CSA and Major Depression (MD), with odds ratios (ORs) typically ranging from 2.1 to 7.0 (Jumper 1995, Neumann et al. 1996, Rind and Tromovitch 1997, Fergusson et al. 1996, Kendler et al. 2000, Paolucci et al. 2001, Putnam 2003, Kaplow and Widom 2007, Young et al. 2007, Bonomi et al. 2008, Carey et al. 2008, Draper et al. 2008, Fergusson et al. 2008, Rohde et al. 2008, Powers et al. 2009, Chen et al. 2010). Furthermore, two studies have applied the co-twin control method to this question and found significantly increased rates of MD in the exposed versus unexposed twin, thereby substantially increasing the probability that the CSA–MD association is causal (Kendler et al. 2000, Nelson et al. 2002).

The association of CSA with risk of MD has been extensively documented in Western populations as has the general dose–response relationship between CSA and risk for developing MD. The finding that CSA involving intercourse is the most strongly associated with risk for MD is also quite robust (Mullen et al. 1996, Fergusson and Mullen 1999, Fleming et al. 1999, Jonas et al. 2011). These results have been confirmed by Cong et al. in the Chinese population (Cong et al. 2011). CSA was found to have a positive «dose–response» relationship with risk for MD: the greater the severity of CSA, the stronger the observed association with MD. Studies including both men and women have shown less consistent results, but some evidence suggests that women with histories of CSA may be more likely to suffer from depression in adulthood than men who have been victims of CSA (Weiss et al. 1999). Many researchers have explored the nature of the relationship between CSA and subsequent adult development of MD (Browne and Finkelhor 1988). However, it is unclear why some survivors develop particular symptoms with varying degrees of severity, while others do not. In order to further investigate this phenomenon, researchers have found that some specific characteristics of the abuse itself account for the variance in symptom formation among survivors (Alexander 1993, Boudewyn and Liem 1995). In an endeavor to help predict which survivors develop depression, specific abuse characteristics have been investigated as related to depressive symptomatology development following CSA. Different characteristics of abuse could influence the risk for negative adult psychosocial outcomes These characteristics include severity, the age of the child, the relationship to the perpetrator. In particular, the presence of coercion or violence, younger age at the time of the event, and abuse by a family member are associated with the most debilitating effects (Loeb et al. 2002, Wyatt et al. 1999, Wyatt et al. 2004, Myers et al 2006, Dong et al. 2003, Lange et al. 1999, Messman-Moore et al. 2000, Smith et al. 2000, Zanarini et al. 2002, Zink et al. 2009).

Childhood Physical Abuse (CPA) is also related to the development of a mood disorder, even if there are fewer studies compared to CSA. Among women with MD, the prevalence of reported CPA (40.3%) is almost double than the one found within the larger sample of women from which it was drawn (21.1%) (Macmillan et al. 1997). Findings from the study by McHolm et al. demonstrated that a history of childhood physical abuse may be most closely associated with suicidal ideation (McHolm et al. 2003) Depressed women who had experienced CPA were almost three times more likely to experience suicidal ideation in their lifetime. Mood disorder patients with history of CPA had an increased suicide risk during the episode and reported a greater number of suicide attempts in the past, compared to patients without CPA (Serretti et al. 2013).

Childhood Emotional Neglect may be a stronger predictor of some dimensions of psychological functioning in young adults than physical abuse (Gauthier et al. 1996). Neglect was significantly related both to increased psychological problems and to difficulties in relationships with others. Individuals who reported having been neglected were more likely to report current symptoms of anxiety, depression, somatization, paranoia, and hostility than were those who reported only physical abuse. Spinhoven et al. (2010) reported that emotional neglect is specifically related to dysthymia, major depressive disorder and social phobia. Individuals with a history of emotional neglect and to a lesser extent sexual abuse are more likely to develop more than one lifetime affective disorder (Spinhoven et al. 2010).

Childhood Emotional abuse (CEA) has been associated with the development of depressive symptoms and clinical depression in several studies (Hankin 2006, Teicher et al. 2006, Yamamoto et al. 1999, Igarashi et al. 2010, Chapman et al. 2004, Gibb et al. 2001, Rich et al. 1997, Spasojevic and Alloy 2002, Bifulco et al. 2002, Gibb et al. 2003). In addition, there is some evidence for the relation between a history of childhood emotional abuse and the presence of anxiety disorders, particularly social phobia, in adulthood (Harkness and Wildes 2002, McCabe et al. 2003). Rose and Abramson hypothesized that childhood emotional abuse may contribute specific vulnerability to the development of depression, suggesting that childhood emotional abuse should be more likely to contribute to the development of a cognitive vulnerability to depression than either childhood physical or sexual abuse because with emotional abuse the depressive cognitions are directly supplied to the child by the abuser (Rose and Abramson 1992). Once developed, this cognitive style is hypothesized to contribute specific vulnerability to depression as opposed to other disorders. In support of Rose and Abramson's theory, there is some evidence for the specificity of emotional abuse to depressive cognitions (Gibb 2002).

A recent meta-analysis suggested that maltreated individuals are twice as likely as those without a history of childhood maltreatment to develop both recurrent and persistent depressive episodes (Nanni et al. 2012). Compared with depressed individuals without a history of childhood maltreatment, depressed and maltreated individuals benefit less from treatment, thereby incurring greater risk of recurrent and persistent depressive episodes (Nanni et al. 2012).

Childhood Maltreatment and neurobiological correlates of depression

A genetic diathesis (genes, gender, personality, family history) interacting with environmental influences (stress, abuse, neglect, adverse family relations) probably underlie vulnerability for depression (Kendler et al. 2002, Merikangas and Swendsen 1997, Nestler et al. 2002). It is estimated that 30–40% of the risk for depression is genetically determined. Risk factors of depressive disorders include a family history of depression, past episodes of depression, female gender, and neuroticism among childhood maltreatments and others. As noted earlier, childhood maltreatment is a significant risk factor for adult mood disorders. Despite the exposure to significant adversity, some individuals achieve normal adaptation. This observation has conducted to the concept of psychological «resilience», defined as the individual's tendency to cope with stress and adversity (Cicchetti and Rogosch 1997, Luthar et al. 2000, Masten 2001). Resilience is supposed to derive from the complex interaction among neurobiological, social and personal factors (Charney 2004, Feder et al. 2009, Bonanno et al. 2007, Holahan and Moos 1991, Murrell and Norris 1983). Resilience may be negatively influenced by childhood trauma, but it has been found to be relatively high in some populations exposed to disadvantage, trauma and adversity (Simeon et al. 2007, Masten 2001). Not all studies show positive reciprocal correlations between childhood trauma, poor resilience and depressive symptoms (Carli et al. 2011). Childhood maltreatment could explain only 2% of the variance in resilience and the majority of variance remains unexplained (Campbell-Sills et al. 2009).

Childhood programming of neurobiological systems, which are implicated in regulating emotion and stress responses, appears to increase vulnerability and depression risk later in life. Childhood maltreatment is therefore likely to have a negative effect on such neurobiological programming, which can possibly lead to adult psychopathology. We will consider three potential areas of impact of early life stress in humans: (1) on neurobiological systems, (ii) on abnormal brain features and (iii) on cognitive processing of emotional information.

1. Effects of early life stress on neurobiological features

The mechanisms that mediate the impact of early adversity on depression risk have long been studied. Early life stress influences the brain and its stress regulatory outflow systems, including the autonomic, endocrine and immune systems, and it may lead to the development of a vulnerable phenotype. An individual's neurobiological abnormalities could be a marker of vulnerability to recurrent major depression episodes (Hasler et al. 2004, Hasler and Northoff 2011, Flint and Munafò 2007). A better understanding of those neurobiological abnormalities might help to identify individuals at risk of depressive onset or recurrence (Bhagwagar and Cowen 2008).

1.1. Serotonin system

5-HT neurotransmission is altered in depressed patients (Cowen 2005). The efficacy of selective serotonin re-uptake inhibitors in the treatment of depression suggests that low 5-HT activity might be associated with acute and recovered depressed patients. A low 5-HT1A receptor availability could render affected individuals at an increased risk of emotional disorders. Fisher et al. recently demonstrated an increased reactivity of the amygdala to negative facial expressions correlated with lower 5-HT1A receptor binding in the raphe nuclei in healthy subjects (Fisher et al. 2006). Accordingly, low 5-HT1A receptor availability could increase the processing of negative emotional stimuli in limbic regions predisposing individuals to emotional disorders (Vuilleumier 2005). The liability to re-experience depressive symptomatology when undergoing acute tryptophan depletion (ATD), a dietary manipulation that decreases brain 5-HT function, is an important abnormality in depressed patients (Smith et al. 1997, Ruhé et al. 2007). This effect is absent in people who have no history of depression and no personal risk factors, indicating that depressive reactions to ATD are probably associated with a personal history of

major depression. As a result of ATD, the brain seems to acquire an organizational state in which negative emotions are much more readily accessed.

The hypothesis of effects of early life stress and maltreatment on the serotonergic system is based on findings from studies of rhesus monkeys showing that adverse rearing conditions resulted in lower CSF 5-HIAA (Higley et al. 1996a, Higley et al. 1996b) and lower serotonin transporter (5-HTT) availability (Ichise et al. 2006). In humans, it has been found that childhood emotional neglect is associated with low CSF 5-HIAA in abstinent cocaine-abusing adults (Roy 2002) and lower 5-HTT availability in depressed subjects who reported childhood abuse (Miller et al. 2009). Furthermore, Rinne and colleagues (2000) found neuroendocrine evidence for reduced serotonergic neurotransmission in subjects with borderline personality disorder (BPD) with experiences of childhood physical and sexual abuse, and this reduction appeared to be independent of the BPD diagnosis. Taken together, the findings in these studies suggest that childhood maltreatment may reduce serotonergic neurotransmission permanently in various psychiatric disorders.

1.2. Catecholamine system

Another neurobiological feature linked to depression is catecholamines. Catecholamine synthesis inhibitor a-methyl-paratyrosine (AMPT) produces acute depressive relapse of recovered depressed patients (Berman et al. 1999). On the other hand, dietary depletion of the amino acid precursor of noradrenaline and dopamine - tyrosine - does not (McTavish et al. 2005). Tyrosine depletion seems to limit its effect to dopamine activity, probably because of the greater utilization of tyrosine by dopaminergic neurons, while AMPT diminishes both noradrenaline and dopamine synthesis (McTavish et al. 1999). This suggests that the depressive relapse caused by AMPT is due to lowered noradrenaline activity. A PET study of AMPT in recovered depressed showed that similar brain circuitry are involved in ATD-induced depressive relapse (orbitofrontal cortex, dorsolateral prefrontal cortex and thalamus) (Bremner et al. 2003). This circuitry appears to be susceptible to the effects of impaired noradrenaline neurotransmission as well as lowered 5-HT function.

As previously proposed by Roy (2002) in cocaine addicts, adverse childhood experiences, and particularly poor child–parent relationships, appear to negatively influence personality development, possibly contributing to a stable dysfunction of brain monoamines, with an inverse correlation between emotional neglect during infancy and CSF metabolites of serotonin and dopamine in the adult.

1.3. The Hypothalamo–Pituitary–Adrenal Axis

Individuals with major depression usually show increased secretion of cortisol (Holsboer 2000). Also some remitted patients present abnormal hypothalamo–pituitary–adrenal (HPA) axis function, particularly those at high risk of recurrence (Zobel et al. 2001). The waking salivary cortisol is increased both in acute depression and in recovered depressed patients (Bhagwagar et al. 2005, Bhagwagar et al. 2003). A similar increase can be found in also in young people who have a depressed parent, and cannot be explained by symptomatic status, childhood adversity or recent life events (Mannie et al. 2007). One study examined the relationship between trauma, psychiatric symptoms and urinary free cortisol (UFC) and catecholamine excretion in prepubertal children with posttraumatic stress disorder (PTSD) secondary to past child maltreatment experiences. Urinary catecholamine and UFC concentrations showed positive correlations with duration of the PTSD trauma and severity of PTSD symptoms. These data suggest that maltreatment experiences are associated with alterations of biological stress systems in maltreated children with PTSD (De Bellis et al. 1999).

Major depression following childhood abuse is associated with insufficient inhibitory feedback regulation of the HPA axis. Animal models shows that low levels of maternal care are associated with reduced hyppocampal concentration of glucocorticoid receptors (Liu et al. 1997); a similar mechanism may partly explain the observed changes in HPA regulation in humans following maltreatment: abuse increases the risk of developing depression due to a sensitization of the neurobiological systems implicated in stress adaptation and response (Heim et al. 2008). Women with a history of maltreatment (with and without depression) exhibit an increased ACTH response (Heim et al. 2002). A childhood abuse history is a strong predictor of ACTH responsiveness. Heim et al. (2008) reported an increased cortisol response in the context of a failure of the glucocorticoid-mediated negative feedback loop to adequately control HPA activation in a sample of men with and without childhood maltreatment and current depression. Furthermore, HPA function is under the influence of the epigenetic regulation of the glucocorticoid receptor in animals and humans. Interestingly, a recent study observed that suicide victims with a history of childhood abuse had decreased levels of a neuron-specific glucocorticoid receptor (NR3C1) mRNA in the postmortem hippocampus and increased site-specific methylation in the exon 1f NR3C1 promoter suggesting an association between cytosine methylation, transcription factor binding and gene expression (McGowan et al., 2009). These results indicate that adverse life events in childhood may change epigenetic states in relevant genomic regions, the expression of which may influence individual risk for psychopathology.

1.4. The gamma-aminobutyric acid system

The gamma-aminobutyric acid (GABA) system has also been implicated in psychopathology. Ascending 5-HT pathways make synaptic connection with both GABA interneurons and glutamatergic pyramidal neurons in both cortical and limbic regions (Taylor et al. 2003). Depressed patients showed lowered GABA levels in occipital cortex (Sanacora et al. 2004). GABA levels in depressed patients can be increased by SSRI treatment and electroconvulsive therapy (ECT) (Sanacora et al. 2002, Sanacora et al. 2003). The increased GABA levels seem to be an effect of treatment rather than a consequence of clinical recovery. Recovered unmedicated depressed patients shows a lowered GABA levels in occipital cortex, suggesting that diminished GABA availability could be a trait maker of vulnerability to depression (Bhagwagar et al. 2007). One study examined the effects of maternal separation on behavioral responses to novelty and on GABA receptor levels in the rat, suggesting that early life events influence the development of the GABA receptor system, thus altering the expression of fearfulness in adulthood (Caldji et al. 2000).

1.5. Other systems

Some studies provide interesting insights on the relationship between stress and sleep. The sleep polysomnogram (electroencephalogram, EEG) changes in patients at risk for depression has been investigated: acute and recovered depressed patients manifest a short latency to REM sleep and an increased density of REM sleep, suggesting that the regulation of REM sleep is a possible endophenotypic marker of vulnerability to depression (Giles et al. 1993). Individuals reporting CSA show more frequent and more distressing episodes of sleep paralysis (Abrams et al. 2008). In abused child syndrome patients, the main sleep changes are decreased sleep efficiency, decreased sleep onset sleep latency, increased wakefulness, decreased REM sleep and total sleep time. The abused child syndrome shows abnormal sleep patterns, independent of the type of abuse, age or sex (Collado-Corona et al. 2005).

1.6. Gene-environment interactions

Finally, recent genetic studies have proposed gene-environment (GxE) interactions. GxE research provides a potential pathway of understanding how genetic differences may influence the likelihood that exposure to environmental stress will result in psychopathology. Most studies to date have mainly focused on GxE interactions with a promoter polymorphism (5-HTTLPR) found on the serotonin transporter gene (SLC6A4). The original study by Caspi et al. (2003) showed a significant interaction between levels of childhood maltreatment and 5-HTTLPR genotype on depression and suicide. Several replications and non-replications followed. The most-recent meta-analysis concluded that on the basis of evidence to date, there is strong support for the role of the 5-HTTLPR as a moderating factor of the relationship between depression and early life stress (Karg et al. 2011). Furthermore, the moderating effect of 5-HTTLPR may be strongest when adverse experiences have occurred in childhood and the depressive symptoms persist over time, as one study showed an interaction of the short 5-HTTLPR allele and childhood maltreatment on *chronic* course of depression in adulthood (Brown et al. 2012).

These neurobiological changes, taken together, could reflect risk to develop depression after early life stress events. In several studies, these changes were not present in depressed persons without early life stress, suggesting the existence of biologically distinguishable subtypes of depression that could be responsive to differential treatments.

2. Effects of maltreatment/early life stress on brain features

The relationship between maltreatment and emotional disorders could also be understood by investigating the effects of maltreatment on brain features, which could help identify potential risk markers for depression. It is well established that childhood maltreatment causes changes in the hypothalamic-pituitary-adrenal axis responsiveness to stress and could thereby increase the risk for developing depression (Heim et al. 2008, Heim et al. 2000).

2.1. Structural brain changes

Structural changes in maltreated children include smaller brain volumes in general, corpus callosum atrophy and smaller hippocampal volumes in particular (De Bellis et al. 1999). Smaller hippocampal volumes have been observed in MDD, but it is not clear if that reduced volume is a risk factor for or a feature of depression (MacQueen and Frodl 2011, Chen et al. 2010, Amico et al. 2011). Patients who have experienced emotional neglect and physical or sexual abuse as a child show even smaller hippocampal volumes (MacQueen and Frodl 2011, Frodl et al. 2010, Vythilingam et al. 2010). Repeated maltreatment experiences during childhood could sensitize the neuroendocrine stress response leading to hippocampal structural abnormalities (Rao et al. 2010, Heim et al. 2008). There is evidence that these hippocampal volume reductions persist into adulthood, even in healthy subjects (Dannlowski et al. 2012).

Maltreated subjects also show a medial prefrontal cortex volume reduction (van Harmelen et al. 2010, Dannlowski et al. 2012). Amygdala and medial prefrontal cortex are both involved in emotion regulation processes, and an increased risk for depression could be related to the deficits in emotion processing and emotion regulation due to a volume reduction in this area. Further, depressed individuals who suffered maltreatment show a gray matter volume reduction in the bilateral insula, the anterior cingulate gyrus, the orbitofrontal cortex, and the caudate (Slavich et al. 2010, Arnone et al. 2012, Koolschijn et al. 2009).

2.2. Functional brain changes

Functional imaging studies have also explored the role of limbic circuitry in negative affective processing biases in major depression. For example, depression is associated with increased responses in the amygdala, ventral striatum and insula to facial negative expressions of emotion (Surguladze et al. 2005, Fu et al. 2004, Siegle et al. 2007, Sheline et al. 2001, Victor et al. 2010, Suslow et al. 2010, Stuhrmann et al. 2011). Amygdala hyperactivity has been hypothesized to cause negatively biased emotion processing that could be related to the pathogenesis of major depression (Dannlowski et al. 2007, Hamilton and Gotlib 2008). Hyper-activation of the amygdala is also sometimes present in response to happy and neutral faces, although other studies show that the responses to happy facial expressions in the thalamus, amygdala, hippocampus and putamen appear to be reduced (Lawrence et al. 2004, Fu et al. 2007).

Adults reporting childhood emotional abuse and/or neglect showed enhanced amygdala activation in response to emotional facial expressions independent of psychiatric status, neuroticism, depression severity, and history of concurrent physical or sexual abuse (van Harmelen et al. 2012). A positive correlation between childhood physical maltreatment and right amygdala responsiveness to sad facial expressions in depressed individuals has also been recently reported, but the study could not distinguish if this correlation represents a feature of current major depression or a risk factor for depression onset (Grant et al. 2011). Recent findings suggest that non-depressed, but maltreated, individuals show stronger amygdala responsiveness to negative stimuli compared to non-maltreated individuals, exhibiting therefore limbic hyper-responsiveness in a non-depressed maltreated sample (Dannlowski et al. 2012).

3. Cognitive processing of emotional information

The effects of childhood maltreatment on cognitive

functioning have been seldom examined. There is abundant literature, however, showing that cognitive processing of emotional information is impaired in MD. The cognitive theories of depression emphasize the role of negative biases in information processing in the etiology and maintenance of MD. The importance of correcting such biases is considered important to obtain a successful treatment (Beck et al. 1979).

Cognitive processes are not uniformly biased in depression. There is evidence supporting an enhanced selective memory for negative material particularly seen in explicit memory paradigms. For example, patients show a tendency to remember negative rather than positive words when they are asked to recall positive and negative self-descriptors encoded in a classification task (Matt et el. 1992). Depressed individuals are also characterized by negative biases in the correct identification of emotional facial expressions that may contribute to interpersonal problems in depression, representing an important factor in the maintenance of this disorder (Gotlib and Krasnoperova 1998). This impairment is associated with interpersonal difficulties, persistence of depressive symptoms, and relapse after remission of the depressive episode (Feinberg et al. 1986). Depressed individuals' readiness to attend to negative aspects of social surroundings contributes to the decreased levels of social support that those patients experience. A number of studies have examined responses to the human faces expressing emotions, a powerful stimulus that represent salient features of the social environment - helping individuals to avoid conflict, to monitor emotional reactions adjusting their behavior accordingly, and to determine the attitudes of other people (Ekman and Friesen 1976, Hansen and Hansen 1994, Hess et al. 1988, Salovey and Mayer 1990). A negatively biased interpretation of ambiguous textual or visual stimuli has been reported in depression (Leppänen 2006). Depressed individuals made more errors than controls in labeling facial expressions and reported higher levels of distress when they were confronted with these faces (Persad and Polivy 1993). The tendency to label ambiguous angry faces as sad is related to the persistence of a depressive episode 6 weeks after intake, as well as to relapse 6 months after termination of treatment (Bouhuys et al. 1999a, Bouhuys et al. 1999b, Geerts and Bouhuys 1999).

It is not clear if depression is associated with a general deficit in emotion identification or with a bias in the identification of specific emotional expressions. Some studies shows that depressed individuals are characterized by deficits in the processing of all emotional (and neutral) facial expressions, but the researchers are not always concordant (Carton et al. 1999, Cooley and Nowicki 1989, Mikhailova et al. 1996, Ridout et al. 2003, Walker et al. 1984). For example depressed individuals may tend to label neutral faces as sad and happy faces as neutral (Gur et al. 1992, Murphy et al. 1999, Suslow et al. 2001). MDD and healthy individuals identify sad facial expressions with the same intensity. There is evidence for diagnostic specificity of biases in the identification of emotional faces for MDD individuals: they require significantly greater intensity to correctly identify or label happy expressions than non-MDD individuals. MDD participants also require less intense expressions to correctly identify sad than angry faces (Joormann and Gotlib 2006).

Children who have experienced maltreatment may develop a tendency toward a hyper-vigilance to perceived threatening cues that emerged as an adaptive response to actual threats in the past (Dodge 2003). Differential effects on emotion processing have been found for physical abuse versus neglect (Hayward et al. 2005). It seems that individuals with a history of emotional abuse and/or neglect tend to interpret facial expressions as highly salient, responding with amygdala hyper-vigilance (Hayward et al. 2005). Neglected children are reported to have poor valence discriminatory abilities for different facial emotions, and it has been suggested that neglected children may misinterpret all emotional faces as threatening (Pollak et al. 2000, Fries and Pollak 2004, Vorria et al. 2006). A history of physical abuse has been linked to a response bias to perceptions of angry facial expressions, whereas a history of neglect has been found to relate more strongly to difficulty in discriminating emotional expressions and a bias toward sad faces (Pollak et al. 2000). For children who have experienced physical maltreatment, displays of anger in their environment are their strongest predictors of threat; thus, a selective attention to threat-related (i.e., anger-related) signals at the expense of attention to other emotional cues would be adaptive. In contrast, neglect is typically associated with an emotionally impoverished environment, with few opportunities for meaningful social interactions. If children are deprived of interactive emotional experiences with others, their capacity to tolerate intense emotion states, including positive emotions, may be underdeveloped (Lee and Hoaken 2007).

Mayer et al. (2010) found a significant association between level of childhood trauma exposure and cognitive performances of long-term and working memory in a group of healthy adults. Healthy adults with high exposure to emotional abuse exhibited a higher error rate in a working memory test. Furthermore, individuals with high levels of exposure to physical neglect showed a higher error rates in working memory and prolonged latency to a correct response in the recognition memory test. A marginal association between level of exposure to sexual abuse or physical neglect and a lower academic achievement in traumatized subjects was observed (Majer et al. 2010).

In sum, from a behavioral or neural point of view, emotional processing biases are essential to understand vulnerability to depression. Assessing the early identification or labeling of traces of emotion and of subtle changes in facial expressions could yield important information to understand depression-associated deficits in interpersonal functioning. Biases in the identification of emotions in facial expressions may have adverse consequences, given that individuals use others' facial expressions as important cues by which to regulate their own behavior. Assessing such biases in maltreated individuals would also assist in identifying individuals at risk for psychopathology.

Conclusions

Depression is a multifactorial problem, as it consists of predisposing, precipitating and maintating factors. One of the strongest risk factors for developing depression is the experience of childhood maltreatment. The precise mechanism by which childhood trauma may increase the risk for depression remains unclear. We can conclude that the neurobiological, genetic and emotional information processing studies are providing encouraging results. Further research is necessary in refinining the epigenetic and neural changes that occur during early life experiences, in order to be able to construct early diagnostic and prevenetive tools, as well as individually-tailored treatments.

Table 1

Maltreatment	Definition	Yearly Prevalence		Source
Physical abuse	Intentional injury of a child by a caretaker: hitting, shaking, throwing, poisoning, burning or scalding, drowning, suffocating, or otherwise causing physical harm to a child. Physical harms may also be caused when a parent or carer fabricates symptoms of, or deliberately induces, illness in a child (Fabricated or Induced Illness – FII).	UK, US, New Zealand, Finland, Italy, and Portugal	3.7–16.3%	Machado et al. 2007
		Macedonia, Moldova, Latvia, and Lithuania	12.2–29.7%	Sebre et al. 2004
		Siberia, Russia, and Romania	24–29%	Berrien et al. 1995
Sexual abuse	It involves forcing or enticing a child or young person to take part in sexual activities, including prostitution, whether or not the child is aware of what is happening. The activities may involve physical contact, including penetrative (e.g. rape, buggery or oral sex) or non-penetrative acts. They may include non-contact activities, such as involving children in looking at, or in the production of, pornographic material or watching sexual activities, or encouraging children to behave in sexually inappropriate ways.	Non-contact sexual abuse	3.1% (boys) 6.8% (girls)	Fergusson and Mullen 1999, Nelson et al. 2002
		Contact sexual abuse	3.7% (boys) 13.2% (girls)	
		Penetrative sexual abuse	1.9% (boys) 5.3% (girls)	
		Any sexual abuse	8.7% (boys) 25.3% (girls)	
Emotional abuse	Persistent emotional maltreatment of a child such as to cause severe and persistent adverse effects on the child's emotional development (conveying to children they are worthless, unloved, inadequate or only valued to meet the needs of another person; developmentally inappropriate expectations, including overprotection, limitation of exploration and learning, or preventing normal social interaction; witnessing the ill-treatment of another; serious bullying and terrifying, exploitation and corruption). It can also be involve repeatedly taking a child for unnecessary medical treatment, threatened or actual abandonment, serious bullying (including cyber-bullying), causing children frequently to feel frightened or in danger.	US	10.3%	Finkelhor et al. 2005
		Macedonia, Latvia, Lithuania, and Moldova	12.5–33.3%	Sebre et al. 2004
		Cumulative prevalence (Sweden, US and UK)	4-9%.	Gilbert et al. 2009
Neglect	Persistent failure to meet a child's basic physical and/or psychological needs, likely to result in the serious impairment of the child's health or development.	Cumulative prevalence for US and UK	6–11.8%	Theodore et al. 2007

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