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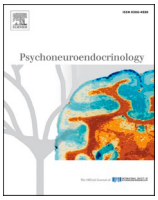

Early traumatic experiences and the hypothalamus-pituitary-adrenal axis in people with eating disorders: A narrative review

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ABSTRACT

Exposure to trauma during childhood is a non-specific risk factor for psychiatric disorders, including eating disorders (EDs), over the life course. Moreover, an association between stressful life events and the onset/maintenance of EDs has been documented. Therefore, the hypothalamus-pituitary-adrenal (HPA) axis, namely the main component of the endogenous stress response system, has been proposed to be implicated in the pathophysiology of EDs. In this narrative review the current knowledge concerning the effects of early trauma exposure on the HPA axis activity and their putative role in the pathophysiology of EDs will be illustrated. Research findings corroborate the idea that childhood trauma exposure has long-lasting dysregulating effects on the activity of the HPA axis, which may contribute to the biological background of the early trauma-related risk for the development of EDs across the life span. Moreover, literature data support the existence of a "maltreated ecophenotype" in EDs characterized by specific clinic and neuroendocrine features, which may have important implications in treatment programming for such a type of patients.

1. Introduction

The exposure to childhood maltreatment increases the risk for development of both physical and mental disorders later in life (Gilbert et al., 2009; Keyes et al., 2012). Indeed, it has been widely demonstrated that different psychiatric disorders, including mood disorders, anxiety disorders, psychosis, alcohol and drug use disorders, disruptive and antisocial behavior disorders and eating disorders (EDs) occur more frequently in adults with a history of childhood trauma exposure than in those without early traumatic experiences (Kisely et al., 2018). Furthermore, the onset of psychiatric disorders across the life course has been associated to adverse childhood experiences in nearly one third of cases, underscoring the public health significance of that exposure (Green et al., 2010; Kessler et al., 2010; Kessler et al., 2011). Because of such an association of adverse early life experiences with the later occurrence of different psychiatric disorders, childhood maltreatment is considered a non-specific risk factor for the development of psychopathology in the adulthood.

A more frequent history of childhood maltreatment has been reported in people with EDs compared to general population (Jacobi et al., 2004; Carter et al., 2006; Caslini et al., 2016). The overall odd of having an ED has been estimated to be 3.21 time higher in individuals reporting a childhood trauma (Caslini et al., 2016). A recent meta-analysis found that the prevalence of childhood maltreatment was higher in each type of EDs (total N = 13 059, prevalence rates 21–59%) compared to both healthy controls (N = 15 092, prevalence rates 1–35%) and psychiatric control groups (N = 7736, prevalence rates 5–46%) (Molendijk et al., 2017). Moreover, distinct types of maltreatment during childhood, such as sexual, physical and emotional abuse or neglect, traumatic loss, and interpersonal stressors have been associated to both the onset and the maintenance of different EDs (Johnson et al., 2002; Su et al., 2016; Larsen et al., 2017; Sanci et al., 2008).

From a clinical point of view, people with EDs and history of childhood maltreatment show more severe symptoms and lower daily functioning, regardless of the presence of psychiatric comorbidities (Guillaume et al., 2016). Moreover, a significant dose-response effect between the number of experienced trauma and ED symptoms severity has been demonstrated (Guillaume et al., 2016). Finally, compared to patients with EDs without a history of childhood trauma exposure those who were exposed to early traumatic events have been shown to exhibit a higher drop-out rate from psychotherapies (Mahon et al., 2001).

Other than clinically, people with EDs and a history of childhood

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maltreatment may biologically differ from those without childhood maltreatment. In fact, a recent study showed that patients with EDs reporting history of childhood maltreatment show reduced grey matter volume in the right paracentral lobule and in the left inferior temporal gyrus as well as an impaired white matter integrity in the corpus callosum, internal capsule, posterior thalamic radiation, longitudinal fasciculus and corona radiata (Monteleone et al., 2017a). Moreover, an association between a history of childhood maltreatment and reduced cortical thinning in brain areas, such as the anterior cingulate cortex, frontal regions and parietal lobule has been detected (Cascino et al., 2022).

Since stressful life events have been found associated with the onset/maintenance of EDs (Jacobi et al., 2004; Pike et al., 2006; Rojo et al., 2006) and individuals with EDs have been shown to have experienced greater adversity over their life course (Krug et al., 2013; Goodman et al., 2014), the endogenous stress response system, especially its main component the hypothalamic-pituitary-adrenal (HPA) axis, has been proposed to play a pivotal role in the pathophysiology of EDs. On the other hand, reciprocal interactions exist between the endogenous stress system and brain circuits regulating functions and/or behaviours, which are likely deranged in patients with EDs such as, for example, appetite (Connan et al., 2003). Furthermore, the above reported brain structural alterations in childhood-maltreated people with EDs are intriguingly located in areas involved in the regulation of HPA axis, and thus may affect the endogenous stress response (Connan et al., 2003).

In this narrative review the current scientific evidence supporting the occurrence of enduring effects of childhood trauma exposure on HPA axis activity and how these effects manifest in people with EDs will be illustrated.

2. Childhood maltreatment and the hypothalamic-pituitary-adrenal axis

In last decades, scientific research has made enormous strides in trying to clarify the biological background through which trauma exposure in the childhood may predispose to the development of psychiatric disorders later in life. A potential emerging picture involves the relationship between early traumatic events and alterations in stress-susceptible brain regions leading to long-lasting dysregulation in the endogenous stress response system (Teicher and Samson, 2016; Chami et al., 2019).

The endogenous stress response system is composed of two main components: the HPA axis and the sympatho-adreno-medullary system. While the sympatho-adreno-medullary system is responsible for the 'quick' response to real or perceived environmental stressors, the HPA axis plays a role in the 'slow' acting system by regulating the secretion of glucocorticoids (Tsigos and Chrousos, 2002). Glucocorticoids increase gluconeogenesis and lipolysis, inducing mobilization of fuel from liver and from white adipose tissue in order to provide the energy necessary to cope with the stressor (Tsigos and Chrousos, 2002). Moreover, glucocorticoids exert negative feedback on the HPA axis activity favouring the termination of the stress response. This feedback limits the time of tissue exposure to glucocorticoids, minimizing their catabolic, lipogenic, anti-reproductive and immunosuppressive effects (Habib et al., 2001; Adam and Epel, 2007).

Pre-clinical studies in rodents and non-human primates have largely elucidated the neuroendocrine effects of early life stressors. In rats and mice, the maternal separation model which consists in repeated and prolonged periods of maternal separation during the first two to three weeks of life, has been employed as a model for child abuse/neglect (Shea et al., 2005). Studies adopting that model showed increased basal levels of corticotropin-releasing hormone (CRH), increased basal and stress-induced adrenocorticotropic hormone (ACTH) release and increased corticosterone release in response to stressors in adult rats subjected to maternal separation (Plotsky and Meaney, 1993; Ladd et al., 1996). These pre-clinical studies suggest that early life adversities can lead to long-term dysregulation of the HPA axis.

Several studies have reported alterations in HPA axis activity in response to changes in stress-related methylation levels of genes regulating the HPA axis functioning. In fact, specific cytosine-phosphate-guanine dinucleotide sequences (CpG sites; that is islands close to or within gene promoters where epigenetic modulation occurs via methylation processes) within the exon 1 F of the glucocorticoid receptor gene *NR3C1* were found positively associated to childhood emotional abuse severity and related to a higher basal HPA axis activity. This HPA axis hyperactivity may reflect an acquired resistance of glucocorticoid receptors involved in the endogenous negative cortisol feedback regulating HPA axis functioning (Farrell et al., 2018). Therefore, early life experiences can influence stress sensitivity over the life course through epigenetic changes in stress-related genes, which may explain why some genetically at-risk individuals are more susceptible to some types of stress-reactive psychopathologies (Hankin et al., 2015).

Moreover, structural and/or functional changes in limbic structures (hippocampus, amygdala) and frontal cortical regions (anterior cingulate cortex), which have a key role in the regulation of HPA axis activity and, thus, contribute to the modulation of the stress response have been claimed to underlie the enduring alterations of the HPA axis in childhood maltreated people. In particular, the hippocampus plays a modulatory role on the HPA axis via projections to the paraventricular nuclei of the hypothalamus (Ulrich-Lai and Herman, 2009) and it can be damaged with extended epinephrine and glucocorticoid release during prolonged stress (Sapolsky et al., 1985). Compared to children who hadn't experienced early adversity children exposed to early adversities have been shown to have smaller hippocampal volumes, which has been associated with lower diurnal cortisol levels (Dahmen et al., 2018). Local neuronal damage and atrophy in the hippocampus may be due to the overexpression of stress hormones during acute phases of experienced adversities, thus leading to hypocortisolism in adulthood (Gunnar and Vazquez, 2001). The amygdala facilitates fear learning by activating the HPA axis and is also influenced by stress-induced glucocorticoid release (Ulrich-Lai and Herman, 2009). An increased volume of the amygdala has been associated to early exposure to maltreatment while a decrease in its size has been associated to later exposure to maltreatment (Whittle et al., 2013). The anterior cingulate cortex is a frontal cortical region that plays a pivotal role in orchestrating the endogenous stress reaction (Hostinar et al., 2014). We recently reported the presence of cortical thinning of the anterior cingulate cortex in a sample of ED women exposed to childhood maltreatment (Cascino et al., 2022). Moreover, the functioning of this area has been found to be attenuated in individuals with a history of childhood maltreatment (Baker et al., 2013), thus increasing the likelihood of endogenous stress system dysregulation. Therefore, exposure to early adversities is considered a major determinant of enduring alterations of brain areas regulating the HPA axis functioning, which may lead to an increased individual sensitivity for the development of trauma-related symptoms (Steudte-Schmiedgen et al., 2016; Schalinski et al., 2019).

A key controversial point of this biological background is represented by the direction of trauma-induced changes of HPA axis functioning, since both increased and decreased HPA axis activity has been described in individuals exposed to childhood maltreatment (Heim et al., 2000; Chrousos, 2009). Indeed, a HPA axis hyperactivity, as expressed by higher circulating cortisol levels, increased ACTH and cortisol responses to psychosocial stressors or endocrine challenges (i.e. dexamethasone suppression test, DST), enhanced cortisol awakening response (CAR), has been described in populations with a history of traumatic events in early life age (Heim and Nemeroff, 2001; Heim et al., 2008; Muhtz et al., 2008; Tyrka et al., 2008; Pesonen et al., 2010; Kumari et al., 2013; Lu et al., 2016; Butler et al., 2017). It has been suggested that the hyperactivation of HPA axis in those people is related to an "insensitive" negative glucocorticoid feedback loop resulting in hypersecretion of CRH by the hypothalamus and of ACTH by the pituitary leading to higher circulating cortisol levels. In contrast, other

authors have documented a HPA axis hypoactivity connected to childhood maltreatment in adults with psychiatric disorders and have reported lower circulating cortisol levels and blunted cortisol responses to psychosocial stressors or endocrine tests (DST, CRH test) in psychiatric patients with a history of childhood maltreatment (Carpenter et al., 2009a; Carpenter et al., 2009b; Carpenter et al., 2011; Hinkelmann et al., 2013; Suzuki et al., 2014; Voellmin et al., 2015). In this case it has been proposed that the diminished HPA axis activity may represent the physiologic expression of the hypersensitivity to the negative glucocorticoid feedback or may be due to a long-lasting drop in glucocorticoid catabolism leading to higher active cortisol persistence in liver and kidney without elevation in the periphery (Yehuda and Seckl, 2011).

Different factors could modulate the impact of childhood maltreatment on HPA axis determining the direction of the trauma-induced changes in its activity. First, childhood traumatic experiences are probably associated with a different impact on HPA activity according to the specific neurodevelopmental period of exposure. Indeed, a preclinical study in adult rats subjected to the maternal separation found that maternal deprivation on the first perinatal days produced adult rats with hyperreactive ACTH secretion whereas those deprived at later perinatal days showed a hyporeactive ACTH response to saline injection (van Oers et al., 1998). Second, the time since the trauma exposure may explain the opposite polarities of HPA axis dysregulation (Steudte et al., 2011), since recent trauma exposure has been related to an enhanced HPA axis activity whereas remote trauma exposure has been associated to HPA axis hypoactivity (Yehuda and Seckl, 2011). As a matter of fact, 8–12 year old children with personal history of trauma have been shown to exhibit an enhanced cortisol reactivity to laboratory stress procedures (Ivanov et al., 2011) whereas 12–16 years old female youths exposed to childhood maltreatment exhibited a reduced cortisol reactivity (MacMillan et al., 2009; Trickett et al., 2014). Third, different types of childhood maltreatment may have opposite effects on HPA-axis functioning. In particular, physical abuse has been found associated with faster cortisol reactivity to acute stressors while emotional abuse has been related to a delayed recovery of cortisol secretion following an acute stressor (Kuhlman et al., 2015). Finally, a dose-dependent effect of traumatic experiences on HPA axis activity has been described, suggesting a higher impairment of HPA axis functioning with increasing traumatic load (Gustafsson et al., 2010; Michels et al., 2012; Monteleone et al., 2018a).

3. HPA axis activity in people with EDs

The HPA axis has been the focus of an extensive research in people with EDs and findings have been exhaustively reviewed elsewhere (Lo Sauro et al., 2008; Culbert et al., 2016; Schorr et al., 2017). Briefly, subjects with anorexia nervosa (AN) have been consistently shown to have elevated basal or mean daily cortisol levels (Culbert et al., 2016) due to the well-known effects of starvation and weight status on HPA axis functioning, even if not all the studies report that increased cortisol levels normalize with body weight gain (Fichter et al., 1986). Instead, more variability exists in results of studies on basal and mean daily cortisol levels in women with bulimia nervosa (BN) (Culbert et al., 2016), although several studies suggested that binge-purging episodes may cause elevated basal and mean daily cortisol levels (Kaye et al., 1989; Weltzin et al., 1991). Moreover, literature data suggest that approximately half of the patients with AN and one third of patients with BN do not suppress cortisol levels after the DST (Schweitzer et al., 1990; Neudeck et al., 2001). In this line, in individuals with BN an association between a history of weight loss and/or AN and non-suppression of cortisol to DST was suggested (Neudeck et al., 2001), highlighting the importance of controlling for a history of “extreme” weight loss when assessing the HPA axis activity in those persons.

Some studies showed that people with AN had an enhanced CAR compared to both individuals with BN and healthy controls (Monteleone et al., 2014) whereas others reported no significant differences among groups (Oskis et al., 2012). The CAR of women with binge-purge subtype of AN has been found to be higher than that of women with the restricting subtype of AN and salivary cortisol levels positively correlated with the degree of binge-purging behaviours (Monteleone et al., 2017b). The enhanced CAR of underweight patients with AN was not found in weight-restored women with AN who exhibited a CAR similar to that of healthy controls, suggesting that weight gain may normalize HPA axis activity in patients with AN (Monteleone et al., 2016).

Another line of research has focused on cortisol reactivity to physical and psychosocial stressors to explore the reactivity of the of HPA axis to an acute stress situation. Those studies have suggested the occurrence of both a blunted or an enhanced or a normal HPA axis reactivity to stressor exposure (Monteleone et al., 2011; Het et al., 2015; Vaz-Leal et al., 2018; Schmalbach et al., 2020). Differences in the clinical characteristics and diagnostic composition of the study samples, in the methodology of stress exposure and in the timing of cortisol assessment may explain such discrepancies.

4. Early traumatic experiences and HPA axis functioning in people with EDs

The effects of childhood maltreatment on the HPA axis functioning in people with EDs has been initially investigated by measuring the cortisol response to the DST. Basurte et al. (2004) conducted a pilot study in 25 individuals diagnosed with EDs and found a significant relationship between cortisol suppression to low-dose (0.25 mg) dexamethasone (DXT) and traumatic history with enhanced suppression of cortisol in those patients with more severe trauma exposure. In a subsequent study, the same research group (Díaz-Marsá et al., 2007) explored the cortisol suppression to 0.25 mg DXT in 52 female patients with EDs (9 with restrictive AN, 14 with binge eating-purging AN and 29 with BN) and found that patients with binge eating-purging AN and with BN had greater percent cortisol suppression than both controls and patients with restrictive AN. Moreover, in the group of patients with binge-purging symptoms (n = 43) cortisol suppression was significantly and positively correlated with the total score of the Childhood Trauma Questionnaire (CTQ) and with the score on the sexual abuse subscale of that questionnaire. Based on those results the authors proposed that a hypersensitive HPA axis response to DST in people with EDs is associated to the presence and severity of childhood traumatic events including sexual abuse. Yilmaz et al. (2012), instead, showed no significant differences in cortisol suppression following the DST between BN patients with or without a history of childhood traumatic exposure and reported no significant association between CTQ scores and cortisol levels following the DST.

The serotonergic modulation of the HPA axis activity relatively to the history of childhood maltreatment has been investigated in bulimic patients by one single study. Indeed, Steiger et al. (2001) measured plasma cortisol level after oral administration of the partial serotonin agonist meta-chlorophenylpiperazine in 26 BN women with a history of childhood abuse, 8 non-abused BN women, 12 non-abused healthy women and 11 abused healthy women. They found that cortisol response to the serotonergic agent was significantly decreased in abused BN women compared to normal eater non-abused women.

Very recently, Meneguzzo et al. (2022) have explored the 24-h urinary free cortisol excretion in a sample of 78 female patients with EDs (49 with AN and 29 with BN) with respect to their history of childhood maltreatment. They found that maltreated patients had 24-h urinary free cortisol levels significantly reduced compared to women without childhood maltreatment with childhood physical abuse being the most significant predictor of the 24-h urinary free cortisol reduction.

The effects of childhood trauma exposure on the salivary CAR have been investigated in people with both AN and BN. In a first study, we (Monteleone et al., 2015) confirmed the occurrence of an enhanced CAR in non-maltreated women with AN compared to both healthy controls and non-maltreated women with BN and showed that people with AN or

BN and positive history of childhood trauma exposure exhibited a statistically significant blunting of CAR compared to non-maltreated groups. Based on those findings we hypothesized that malnutrition and childhood trauma exert opposite effects (increase or blunting) on CAR in AN. Moreover, in a subsequent study, we provided the evidence for a dose-dependent effect of the traumatic load on HPA axis activity in women with EDs (Monteleone et al., 2018a). In fact, people with AN and BN with history of early trauma exposure exhibited a progressive impairment of CAR with increasing the number of reported traumas.

The effects of early trauma on HPA activity have been explored also by a dynamic test (Monteleone et al., 2018b). Compared to both healthy controls and non-maltreated women with AN without childhood trauma exposure, a blunted cortisol response to the Trier Social Stress Test (TSST) was detected in maltreated women with AN who displayed a cortisol increase after the TSST significantly lower, although the overall cortisol production was not different from the other two groups. Since the TSST-induced cortisol increase is an index of the sensitivity of the HPA axis to a challenge test, those results suggested that childhood trauma exposure has detrimental effects on the HPA axis reactivity to a psychosocial stressor in adults with AN.

In another study we explored the cortisol and the emotional reactivity to TSST in a sample of women with AN and BN with and without childhood maltreatment (Monteleone et al., 2021). At difference with the previous findings, a higher overall cortisol production was observed in people with AN, regardless of the presence of childhood maltreatment, and in those with BN who reported childhood emotional trauma (including both emotional neglect and emotional abuse experiences). The physical trauma (spanning sexual abuse, physical abuse and physical neglect) had no effect on the cortisol production. We explained such a discrepancy with our previous findings of a decreased cortisol response to TSST in maltreated women with AN (Monteleone et al., 2018b) by difference in the prevalence of emotional trauma between the two study groups. Moreover, ED people reporting early emotional trauma also showed heightened anxiety, lower levels of hunger and more severe body dissatisfaction in response to the acute social challenge in comparison to non-maltreated people with EDs (Monteleone et al., 2021). In

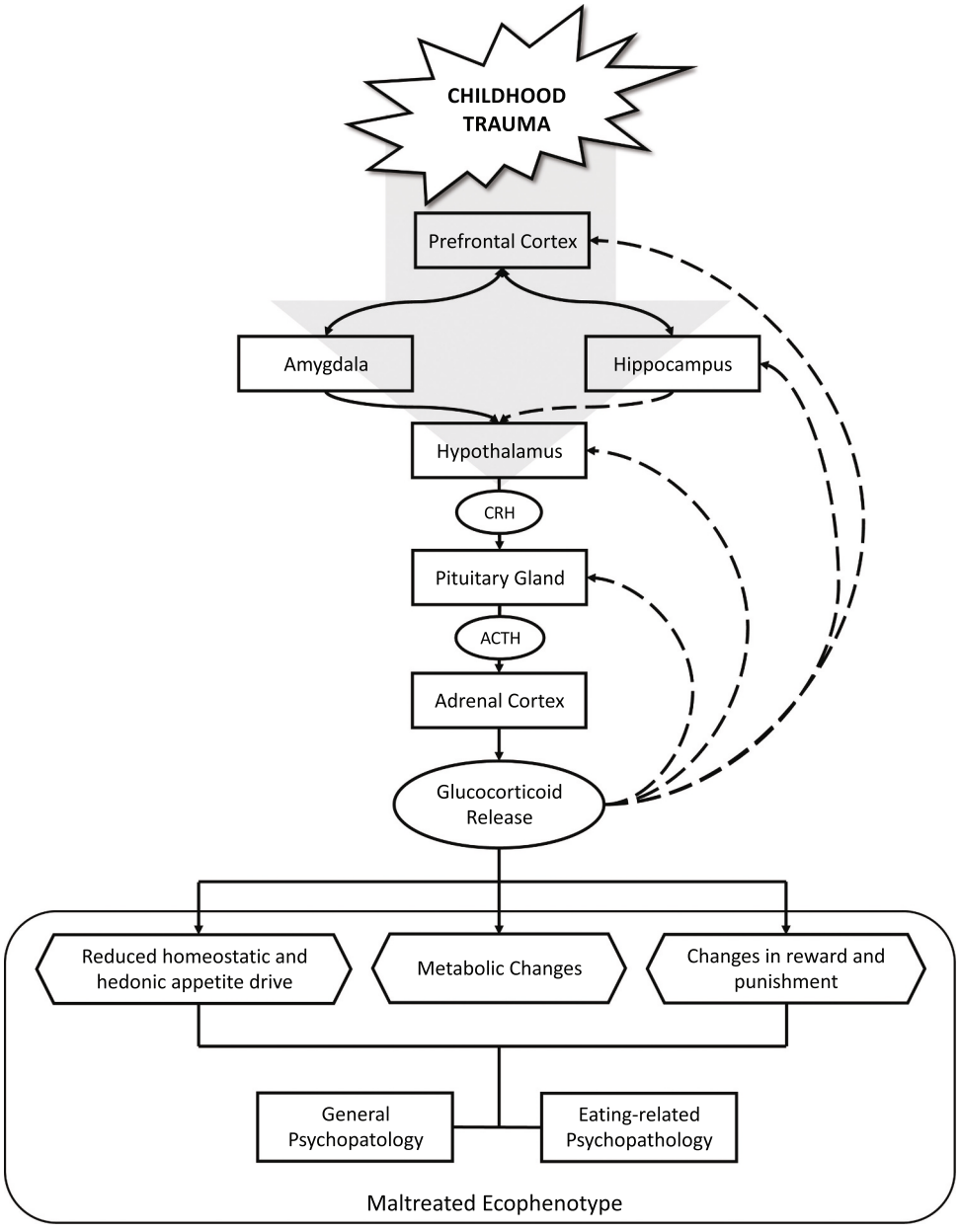

Fig. 1. Schematic representation of the possible role of the HPA axis in the link between trauma and the development of an eating disorder.

sum, emotional trauma was the main type of childhood maltreatment contributing to the experimental differences observed in maltreated people with EDs. The role of emotional trauma in EDs has been further supported by the evidence that emotional abuse connected each type of childhood maltreatment with specific eating symptoms in network analyses conducted in the main ED diagnostic groups (Monteleone et al., 2019; Monteleone et al., 2022).

Finally, one research group has explored the effects of cognitive-behavioural therapy (CBT) on morning plasma cortisol levels in patients with EDs according to the presence of a history of sexual/physical abuse (Lelli et al., 2019). They found that a history of childhood abuse accounted for lower cortisol levels in AN and BN patients, and patients with AN without abuse showed higher cortisol levels. CBT determined a significant reduction of cortisol levels in patients without a history of childhood abuse but not in those with abuse who showed a flattened trajectory in cortisol values between the two time points.

The role of the HPA axis in the link between trauma and the development of an ED is schematically represented in Fig. 1.

5. Early traumatic experiences and psychotherapeutic outcome in people with EDs

Preliminary data seem to suggest that psychotherapeutic interventions have an unsatisfactory outcome in people with EDs exposed to childhood trauma. A recent 3-year observational study assessed whether ED patients reporting childhood abuse (N = 33) had different outcomes to manualized CBT compared to non-abused patients (N = 100). Results show that although ED patients reporting childhood abuse had a more severe clinical presentation at admission with higher psychiatric comorbidity, at the end of treatment no significant difference emerged in the remission rate of any ED between patients with or without a history of abuse. However, at 3-year follow-up ED patients with childhood physical abuse presented a lower improvement of their psychopathology and a lower remission rate of psychiatric comorbid conditions especially mood disorders (Castellini et al., 2018). Furthermore, dropping out for treatment occurred more rapidly in patients with abuse than in those without abuse, and the time to drop-out resulted even shorter in those patients who have experienced both abuse and neglect in their childhood. These findings are consistent with the results of a previous study showing in BN patients exposed to childhood trauma an increasing dropping-out from psychotherapy as the number of childhood trauma increased (Mahon et al., 2001). These data suggest a dose-dependent effect of the traumatic load on the drop-out from psychotherapeutic treatment in BN and recall the above reported finding of a dose-dependent effect of the traumatic load on the CAR impairment in patients with EDs (Monteleone et al., 2018a). At difference with those data, Calugi et al. (2018) reported that the 6- and 12-month clinical outcomes of an enhanced-CBT treatment did not significantly differ between adult AN women reporting childhood sexual abuse and those without history of sexual abuse. Finally, CBT has been shown to be able to improve general psychopathology in non-abused ED patients but not in patients reporting childhood abuse, although in both groups it was equally efficacious in ameliorating eating-related symptoms (Lelli et al., 2019).

6. Conclusions and hypotheses

Research evidence supports the idea that exposure to trauma in the childhood may be responsible of long-lasting effects on the activity of the HPA axis, which could contribute to the biological vulnerability underlying a potential impaired ability to deal with stressful life events in the adulthood. This may favor the development/maintenance of psychiatric disorders, including EDs. Teicher and Samson (2013) suggested that early stressful experiences lead to a developmental phenotype, the "maltreated ecophenotype", characterized by structural and/or functional alterations of multiple brain areas and that may allow to differentiate biologically, other than clinically, individuals with the same psychiatric disorder with respect to their history of childhood trauma exposure. The ecophenotype refers to a phenotypical variation related to specific adaptive response to environmental factors and their interaction with heredity. The above presented data support the existence of a "maltreated ecophenotype" with specific clinical and neuroendocrine features also in patients with EDs, and this may have potential implications for the treatment of AN and BN patients with history of childhood trauma exposure.

Although the research on the clinical implications of early traumatic exposure in patients with EDs is still at its infancy, preliminary findings let us to suggest a lower efficacy of the current therapies primarily focused on ED symptoms in the presence of an history of childhood maltreatment, and corroborate the importance to extend intervention strategies beyond ED core symptoms, focusing on the person's self-esteem development, abilities to recognize inner body states and emotions and on their mediating role between childhood maltreatment and ED symptoms. Since the reported enduring effects of early trauma exposure on HPA axis functioning underlie a greater vulnerability to stressors during the life course, it is plausible that interventions aiming at retuning a deranged HPA axis functioning could potentiate current treatments for childhood traumatized individuals with EDs. In the study from Lelli et al. (2019) a significant reduction of cortisol levels in patients without a history of childhood abuse, but not in those with abuse, was found after treatment with CBT, and the persistence of elevated cortisol levels paralleled the lack of improvement in general psychopathology. However, at present the extent to which interventions specifically aiming at modulating the HPA axis activity could improve the outcome of the available treatments in ED people exposed to childhood maltreatment remains to be demonstrated.

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Declaration of Competing Interest

None.

Data availability

Data sharing not applicable – no new data generated.

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