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Cortisol levels before and after cognitive behavioural therapy in patients with eating disorders reporting childhood abuse: A follow-up study

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ABSTRACT

The etiopathogenesis of eating disorders (EDs) is complex and still not well understood. Biological, psychological and environmental factors (e.g. childhood abuse) have all been considered to be involved in the onset and the persistence of EDs. The hypothalamic-pituitary-adrenal (HPA) axis is a relevant biological factor capable of influencing the onset and the course of EDs and not many information are available about the impact of a Cognitive Behavioral Therapy (CBT) on cortisol changes in EDs. The HPA-axis functioning has been evaluated before and after CBT in a group of patients with Anorexia Nervosa (n = 34) and Bulimia Nervosa (n = 35) according to the presence/absence of a history of sexual/physical abuse. At baseline, only patients reporting childhood abuse showed lower morning cortisol levels as compared with other patients of the same diagnostic group and Healthy Controls. After CBT, a variation of cortisol levels has been found only in patients without abuse, suggesting a role of childhood adversities in the persistence of HPA-axis alterations in Eating Disorders.

1. Introduction

Childhood abuse and neglect are relevant risk factors for adult psychopathology, and in particular for eating disorders (EDs) (Jacobi et al., 2004; Wonderlich et al., 2007; Caslini et al., 2016; Guillaume et al., 2016; Steine et al., 2017; Molendijk et al., 2017; Castellini et al., 2018). Available animal and human data suggest that early traumatic events can induce persistent changes in HPA-axis activity (Nemeroff, 2004; Tarullo and Gunnar, 2006). The hypothalamic-pituitary-adrenal (HPA) axis and the efferent sympathetic/adrenomedullary system represent the means via which the brain influences all the body's organs and functions during exposure to stressful, threatening stimuli, such as childhood and physical abuse (Lo Sauro et al., 2008). As Kuhlman et al. (2017) exhaustively describe for the developmental psychoneuroendocrine and psychoneuroimmune pathways from childhood adversity to disease, exposure to physical abuse and trauma during childhood could exaggerate both inflammatory activity and HPA-axis reactivity to stress until adulthood. Consistently with this hypothesis, childhood physical abuse exposure may be associated with a multi-systemic biological risk profile (Friedman et al., 2015). Several complex neurobiological abnormalities have been reported to be linked with HPA-axis modification, such as the reduced expression of glucocorticoid receptors in the hippocampus, probably due to epigenetic regulation induced by early adversities, which may presage increased expression of corticotropin-releasing hormone in the hypothalamus and exaggerated adrenocorticotropic hormone and glucocorticoid responses to stress in adulthood (Liu et al., 1997; Anacker et al., 2014; McGowan et al., 2009). Dahmen et al. (2018) have reported data about the effects of early-life adversity on hippocampal structures and HPA-axis functions. Children exposed to early adversity showed a smaller hippocampal volume, significantly associated with lower diurnal cortisol than in control children, thus representing a precursor of the vulnerability to mental disorder later in life. It has been hypothesized that local neuronal damage and atrophy in the hippocampus could be due to an over-expression of stress hormones with elevated cortisol levels in acute phases of extreme adversity, and contribute to the development of hypocortisolism in adulthood (Gunnar and Vazquez, 2001). HPA-axis dysregulation (both increased or decreased activity) has also been reported in patients with EDs (Lo Sauro et al., 2008; Castellini et al., 2012, 2013; Monteleone et al., 2015, 2017; Föcker et al., 2016). These contradictory accounts of the direction of HPA-axis activity can be attributed to various methodological factors in research studies in this field, such as: different methods applied in the evaluation of the HPA axis; incomplete information in the assessment of a history of childhood abuse; the amount of time that has passed since the trauma exposure; incomplete information about other psychiatric comorbidities; and different phases of illness (acute phase of AN or BN vs. remission). In fact, it is possible to hypothesize that malnutrition, weight loss and acute stress linked to the acute and a severe phase of illness (both for AN and BN), as well as the presence of recent trauma exposure, could

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determine an increase in cortisol levels; on the other hand, remission from eating disorders, with weight recovery and absence of bingeing/purging behaviors, and distant trauma exposure (i.e. childhood trauma) could account for HPA-axis hypoactivity with low cortisol levels (Lo Sauro et al., 2008; Monteleone et al., 2017; Steudte et al., 2011). Moreover, body-image distortion and pathological eating habits (e.g. eating restraint and bingeing/purging), as well as emotional dysregulation, could determine a constant alertness and stress condition that may influence HPA functioning. From this bidirectional perspective, the problem of whether these modifications are a consequence of the EDs or sustain them remains to be better understood (Scantamburlo et al., 2001). Monteleone et al. (2015) have suggested that symptomatic Anorexia Nervosa (AN) and Bulimia Nervosa (BN) patients with a history of childhood trauma exhibit an attenuated salivary cortisol awakening response (CAR) compared with matched symptomatic patients without such a history (Monteleone et al., 2015), with a possible dose-dependent effect between the number of trauma events and the CAR (Monteleone et al., 2018a). Moreover, Monteleone et al. (2018b) found a significantly decreased saliva cortisol response to the Trier Social Stress Test in women with AN reporting childhood maltreatment, compared to both women with AN and healthy women without a history of childhood trauma exposure. Steiger et al. (2001) have previously reported that BN patients with a history of childhood abuse showed decreased plasma cortisol levels relative to non-abused patients, and that childhood abuse may more specifically be linked to reduced cortisol levels. As already suggested by Montelone et al. (2015), it is possible to hypothesize that malnutrition and early maltreatment may have opposite effects on HPA-axis function in AN and BN, with lower cortisol levels in patients reporting childhood trauma.

Cross-sectional studies (Montelone et al., 2016) do not allow for establishing a cause-consequence relationship between eating disorder psychopathology, HPA functioning and weight status, nor for evaluating the role of early traumatic experiences in terms of state/trait alterations of HPA functioning. Follow-up data about cortisol levels (Herpertz et al., 2000; Lo Sauro et al., 2008; Wild et al., 2014) are controversial, but mainly report increased cortisol levels in the acute phase of AN and normalization after weight recovery without evaluation of potential differences between maltreated and non-maltreated patients.

Cognitive behavioral therapy (CBT) has been found to reduce specific symptoms (Linardon et al., 2017) as well as general psychopathology in patients with EDs (Fichter et al., 2008; Wonderlich et al., 2012; Milos et al., 2013; Castellini et al., 2018). As a possible mechanism, it is feasible that the reduction of psychopathology would determine a normalization of cortisol levels as a consequence of stress reduction. Indeed, the HPA system's functioning has shown to be sensitive for cognitive behavioral interventions in both patients with somatic and mental illness. For example, in patients suffering from human immune deficiency virus (HIV) or breast cancer, cognitive behavioral stress management has been shown to reduce cortisol levels (Antoni et al., 2000; Cruess et al., 2000). In patients affected by PTSD (Bergen-Cico et al., 2014), a significant change in cortisol (e.g., reduction in CAR) has been associated with clinical improvement of the disorder after a cognitive behavioral psychotherapy intervention, such as a brief primary care mindfulness-based stress reduction that was designed to enhance emotional regulation and cognitive reappraisal of stressors. Bergen-Cico et al. (2014) also suggest the use of biomarkers such as cortisol as an objective measure of responsiveness to PTSD treatment after psychotherapy, and concluded that the use of diurnal cortisol measures to assess PTSD-related HPA function may provide health-care professionals with a useful objective measure. Researchers have found that decreases in psychological distress symptoms are accompanied by reductions in diurnal cortisol levels, suggesting that these concomitant changes indicate improved regulation of the HPA axis (Marcus et al., 2003; Olff et al., 2006). Furthermore, cognitive behavioral interventions have been shown to be effective in reducing cortisol levels in adults with other anxiety disorders, in particular, specific phobia (Brand et al., 2011), and generalized anxiety disorder (Rosnick et al., 2016). However, considering the role of childhood abuse as a moderator of treatment in EDs, Castellini et al. (2018) have recently reported that CBT is not fully efficacious in reducing general psychopathology in ED patients reporting a history of childhood abuse, hypothesizing that CBT did not adequately challenge the severe psychopathological consequences of childhood abuse, such as emotional dysregulation. To our knowledge, few data are available about the effect of CBT on cortisol levels in eating disorders, and none of the available studies explored the longitudinal changes of cortisol levels in ED patients after CBT, considering the role of childhood trauma as a potential moderator of this variation. The aim of the present study was to evaluate the relationship between cortisol levels and childhood abuse in EDs, and the impact of CBT on cortisol levels in ED patients with and without a history of sexual/physical abuse. On the basis of the evidence reported above, the following can be hypothesized: (1) patients affected by AN and BN reporting a history of childhood abuse should report lower basal cortisol levels with respect to AN and BN without early maltreatment and controls; (2) CBT should determine a significant reduction of cortisol levels, as a consequence of stress reduction, similarly to the previously described mechanisms for anxiety disorders, only for those patients without history of abuse; while (3) it can be hypothesized that CBT would not challenge the HPA-axis abnormalities in patients with abuse, thus resulting in a persistence of hypocortisolism from baseline to follow-up time after CBT in patients with childhood abuse.

2. Methods

The study was performed at the Outpatient Clinic for Eating Disorders of the University of Florence, Italy. Participants were recruited by referrals from family doctors and other clinicians. All the participants were asked to provide their written informed consent. The study protocol was approved by the ethics committee of the institution.

2.1. Participants

Patients attending the Clinic for Eating Disorders of the Florence University School of Medicine continuously between May 2012 and October 2013 were enrolled in the study, provided that they met the following inclusion criteria: age between 18 and 60 years and current DSM-IV diagnosis of AN or BN, assessed by means of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). Exclusion criteria were as follows: BMI lower than 14 kg/m^2 (patients with a weight status lower than this threshold were considered unsuitable for psychotherapy and were referred to an inpatient treatment); comorbid schizophrenia, bipolar I disorder, illiteracy and intellectual disability; severe medical conditions that preclude outpatient treatment, such as severe heart, renal and/or liver failure; and current use of psychoactive medications, with the exception of antidepressant medication and benzodiazepines, which were kept stable during the study. Additionally, since a significant effect on cortisol levels has been shown for pregnancy (De Weerth and Buitelaar, 2005), some types of brain damage (Buchanan et al., 2004; Wolf et al., 2005), specific endocrinological disorders like Cushing's or Addison's diseases (Adam and Kumari, 2009; Roa et al., 2013) and use of steroid-based medications (Masharani et al., 2005), patients with at least one of these conditions were excluded. These indications have also been successively included in recent expert consensus guidelines regarding cortisol assessment (Stadler et al., 2016).

Of the 90 Caucasian cases with AN or BN, 21 subjects were excluded from the study because of the following reasons: comorbid schizophrenia ($n = 1$ patient), comorbid bipolar I disorder ($n = 3$ patients), illiteracy ($n = 1$ patient), intellectual disability ($n = 1$), BMI of < 14 kg/m^2 ($n = 3$ patients), severe medical conditions ($n = 4$ patients)

and medication not allowed for the protocol (n = 8). The final sample consisted of 69 patients with EDs (34 AN, 35 BN). Seventy-two age and gender-matched healthy controls (HC) were also recruited according to the following criteria: absence of a history of sexual/physical abuse; and absence of any psychiatric disorders according to SCID. Power calculation analyses estimated that a sample size of 14 patients for each group was required to have a power of 80% (considering cortisol levels as an index variable).

2.2. Study design

The clinical assessment and the blood cortisol sampling was performed on the first day of admission (baseline: T0) and repeated at the end of an individual CBT treatment (T1). At T1, the patients were contacted by phone and invited to the clinic for the follow-up visit.

2.3. Assessment

The clinical assessment consisted of a face-to-face interview by two expert psychiatrists in the field of ED treatment (V.R. and G.C.) who had no therapeutic relationship with the participants on the first day of admission (baseline: T0), and was repeated at the end of the individual CBT treatment (T1), one year after the first assessment. Anthropometric measurements were made using standard calibrated instruments during the routine psychiatric visits. The Structured Clinical Interview for DSM-IV (First et al., 1995) was applied in order to identify Axis I psychiatric disorders. The assessors who conducted the diagnostic assessment were blind to the abuse status. The psychometric tests adopted were the EDE-Q (Fairburn and Beglin, 1994) (Cronbach's α = 0.86), used to assess eating attitudes and behaviors; the SCL 90-R (Derogatis et al., 1973) (r = 0.78–0.90), used to assess general psychopathology; and the Childhood Experience of Care and Abuse Questionnaire (Bifulco et al., 2005) (Cronbach's α = 0.80; the accuracy for detecting abuse by means of a dichotomous score was 80% for physical abuse and 72% for sexual abuse screening), in order to evaluate physical and sexual abuse before the age of 17 years old.

Blood samples were drawn in the morning (8 a.m.) after an overnight fast to determine cortisol levels (expressed as nmol/L). Since cortisol levels could be influenced by the use of common substances of abuse (Kudielka et al., 2009), food consumption (Gibson et al., 1999; Rohleder and Kirschbaum, 2007; Rosmond et al., 2000) and physical exercise (Hill et al., 2008; Kirshbaum and Hellhammer, 1994; Stadler et al., 2009), we asked our patients to abstain from smoking, drinking caffeinated or sugared drinks and physical exercise. Furthermore, we made sure that all patients had slept at least seven nights according to a regular day-night schedule, and were not acutely ill or in the ovulation phase of the menstrual cycle when blood samples were drawn, since those factors have also been shown to alter cortisol levels (Adam and Kumari, 2009; Stadler et al., 2016). The same cortisol blood sampling methodology was adopted at the baseline and at the follow-up time.

2.4. Treatment

Patients were provided with an individual CBT program applying validated behavioral and cognitive strategies for patients with AN (Garner et al., 1997; Pike et al., 1996; Fairburn et al., 2003) and BN (Fairburn et al., 1993, 2003). According to the trans-diagnostic treatment theory of eating disorders proposed by Fairburn et al. (2003), a network of inter-related maintaining mechanisms (i.e.: a central cognitive disturbance characterized by the over-evaluation eating, shape and weight and their control) accounts for the onset and persistence of AN and BN. The treatment was provided in two versions, a 20-session treatment for patients affected by BN, and a 40-session treatment for patients affected by AN who are significantly underweight: the longer treatment also includes procedures designed to help patients regain weight. The style and content of the two versions are essentially the same and are comparable. Considering patients with AN, we provided an individual CBT consisting of about 40 one-hour manual-based sessions conducted over a minimum of 40 weeks. Patients with BN were treated with an individual CBT, according to the manual of Fairburn et al. (2003). CBT for BN was composed of 19 visits of 50 min each, over a period of 20 weeks. The actual length of treatment was (m ± sd) (40.32 ± 2.76) weeks for AN and (20.37 ± 2.19) weeks for BN. Five therapists took part in the present study. They are psychiatrists who have completed a four-year training in CBT and are experienced in treating individuals with EDs (Castellini et al., 2018).

2.5. Statistical analyses

The first set of analyses was performed by comparing groups in terms of different clinical variables at baseline, according to the different categorizations (patients vs. healthy controls; AN vs. BN; patients with and without a history of childhood abuse). For between-group comparisons, chi-square and independent measures t-tests were applied for categorical and continuous variables, respectively.

ANOVA was adopted to compare baseline variables among different groups (AN with and without abuse, BN with and without abuse, healthy controls). Pearson's correlations were adopted to evaluate univariate associations between clinical variables. Furthermore, a moderation analysis of cortisol levels was performed at baseline, testing the interaction of diagnosis (AN vs. BN) by a history of childhood abuse.

Linear mixed models (ANOVA mixed model with random intercept) were adopted to evaluate factors associated with variation (time effect) of cortisol levels. Cortisol levels were entered as dependent variables for each model, and time was entered as an independent variable, together with age and baseline values as covariates. In order to test the moderation effect, diagnosis (AN vs. BN) and history of childhood abuse (presence vs. absence of abuse) were entered into each model as independent variables. For each model, we considered random subject-level effects, as well as moderator variables (diagnosis or history of abuse) as fixed effects. Interactions between fixed effects were also considered. Finally, the variation (time effect) of cortisol levels and other clinical variables was evaluated within each group (AN with abuse, AN without abuse, BN with abuse, BN without abuse).

3. Results

3.1. Clinical characteristics at baseline

The final sample consisted of 69 patients (34 AN, 35 BN) and 72 healthy control (HC) subjects matched for sex, age and education level (Table 1 reports the sociodemographic and clinical characteristics of the sample at baseline). Considering the substantial co-occurrence of sexual and physical abuse in our sample [30.4% and 46.3% of ED patients reported sexual (n = 21) and physical abuse (n = 32), respectively; 95.2% of patients with sexual abuse also reported physical abuse (n = 20)], we considered one single dichotomous variable for presence/absence of any form of abuse. At baseline, ED-specific psychopathology (EDE.Q) and general psychopathology (SCL-90) differed significantly between patients and controls, whereas no significant differences were observed between AN (either with or without abuse) and BN (either with or without abuse), with the exception of BMI (significantly lower in AN), age at onset (significantly lower in AN and BN with abuse compared to AN and BN without abuse) and neglect (CECA-Q) (significantly higher in AN and BN with abuse compared to AN and BN without abuse and HC). Patients with AN reported significantly higher baseline cortisol levels with respect to patients with BN (t = 4.22, p < 0.001). Overall, patients with abuse reported lower baseline cortisol levels compared to patients without abuse (t = 5.19, p < 0.001). A general linear model showed that the interaction of diagnosis (AN vs. BN) by a history of abuse was not significant (F = 0.52; p = 0.47).

On the other hand, patients without abuse showed higher baseline

Table 1
Baseline characteristics of the sample.

	AN without abuse (n = 18)	AN with abuse (n = 16)	BN without abuse (n = 18)	BN with abuse (n = 17)	Healthy control (n = 72)	F
Age (years)	25.8 ± 7.1	24.8 ± 8.2	28.5 ± 7.7	25.7 ± 6.8	27.8 ± 6.3	1.63
Education (years)	13.0 ± 3.0	11.4 ± 2.8	11.1 ± 3.9	12.4 ± 2.7	12.1 ± 2.7	1.92
Age at onset (years)	22.4 ± 4.6	19.5 ± 5.0[a]	24.4 ± 6.0	20.1 ± 4.3[a]	–	5.41
Illness duration (years)	3.4 ± 3.9	5.3 ± 5.2	4.0 ± 3.3	5.5 ± 5.5	–	1.51
BMI (kg/m^2)	15.4 ± 2.7[b]	15.8 ± 2.3[b]	24.1 ± 4.5	23.0 ± 4.4	21.6 ± 2.1	54.3
SCL-90 GSI	1.3 ± 0.7[b]	1.6 ± 0.6[b]	1.2 ± 0.5[b]	1.7 ± 0.6[b]	0.4 ± 0.4	27.4
EDE-Q total score	3.0 ± 1.5[b]	3.0 ± 1.8[b]	3.3 ± 1.0 [b]	3.3 ± 1.4[b]	0.9 ± 0.8	34.5
EDE-Q restrain	2.6 ± 1.7[b]	3.4 ± 2.1[b]	2.8 ± 1.6 [b]	2.7 ± 1.6[b]	0.9 ± 1.0	14.1
EDE-Q eating concern	2.8 ± 1.5[b]	2.7 ± 1.7[b]	2.9 ± 1.5[b]	3.0 ± 1.8[b]	0.3 ± 0.4	32.1
EDE-Q weight concern	3.1 ± 1.7[b]	2.8 ± 2.0[b]	3.5 ± 1.4[b]	3.6 ± 1.8[b]	1.0 ± 1.0	24.0
EDE-Q shape concern	3.7 ± 1.8[b]	3.1 ± 1.9[b]	4.2 ± 1.1[b]	4.2 ± 1.9[b]	1.2 ± 1.1	32.9
Cortisol 8 a.m. (nmol/L)	706.4 ± 165.5	412.6 ± 164.3[a]	472.1 ± 132.1	312.8 ± 95.3[a]	528.8 ± 167.9	17.2
Mother Neglect (CECA-Q)	12.3 ± 9.5	18.8 ± 9.2[a]	9.5 ± 6.5	21.9 ± 5.5[a]	9.8 ± 6.5	14.2

Statistics: continuous data are reported as mean ± standard deviation.
Abbreviations: AN, anorexia nervosa; BN, bulimia nervosa; BMI, body mass index; EDE-Q, eating disorder examination questionnaire; SCL-90 GSI, symptom checklist 90 global severity index, CECA.Q, childhood experience of care and abuse questionnaire.
Bonferroni post-hoc analyses.
[a] AN with abuse and BN with abuse respect to AN without abuse and BN without abuse: $p < 0.01$.
[b] Patients groups respect to healthy controls: $p < 0.001$.

cortisol levels compared to HC. No significant correlation was detected between cortisol levels and BMI, age, age of onset and EDE.Q or SCL-90 scores (data not shown). No significant correlation was found between cortisol levels and mother neglect, measured continuously by means of the CECA-Q subscales for neglect (data are not shown).

3.2. Variables associated with variations of cortisol levels

Fig. 1 showed cortisol variation across time after treatment. History of childhood abuse was found to be a moderator of cortisol variation after CBT (abuse by time effect: $F = 32.0$, $p < 0.001$), while the diagnosis was not found to moderate cortisol variation (diagnosis by time effect: $F = 0.52$, $p = 0.47$). Indeed, only patients without abuse reported a reduction of cortisol levels (time effects for AN without abuse, $b = 306.9$, $p < 0.001$; BN without abuse, $b = 251.2$, $p < 0.001$), while patients with abuse did not report any significant change (time effects for AN with abuse, $b = 64.5$, $p = 0.10$; BN with abuse, $b = 5.5$, $p = 0.81$). Moreover, the three-way interaction diagnosis by abuse by time was found not to be significant, demonstrating that the main effect on cortisol reduction was associated with the presence of abuse and not with the diagnosis.

Finally, no significant effect was detected when considering the age of onset, EDE-Q and SCL-90 baseline scores as the potential moderator of cortisol changes (data not shown).

3.3. Psychopathology variations across time

No significant difference was detected, in terms of remission from any ED, between AN and BN (44.3% vs. 52.8%; chi square = 0.95, $p = 0.32$) or between patients with and without childhood abuse (48.0% vs. 51.5%; chi square = 0.12, $p = 0.72$). No significant effect on cortisol variation was detected for remission from any ED ($F = 0.43$;

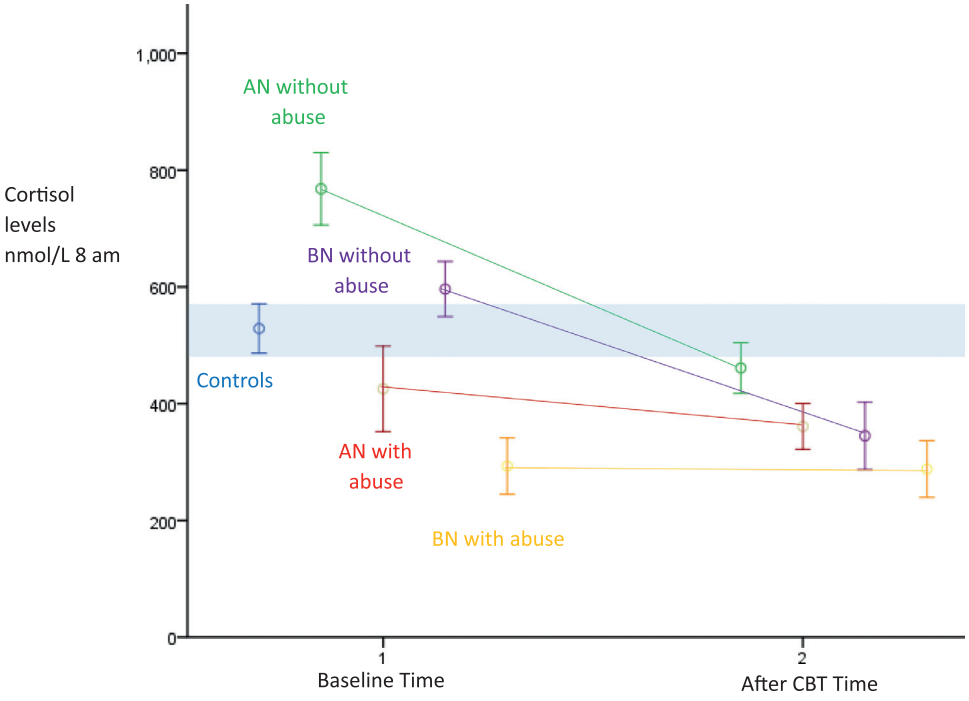

Fig. 1. Cortisol variation across time after treatment. Patients without abuse reported a reduction of cortisol levels (time effects for: AN without abuse, b = 306.9, $p < 0.001$, BN without abuse, b = 251.2, $p < 0.001$), while patients with abuse did not report any significant change (time effects for: AN with abuse, b = 64.5, $p = 0.10$; BN with abuse, b = 5.5, $p = 0.81$). Abbreviations: AN: Anorexia Nervosa, BN: Bulimia Nervosa, CBT: Cognitive Behavioural Therapy.

$p = 0.83$).

At the end of treatment (T1), all patients showed a reduction of EDE.Q total scores (time effects for AN without abuse, $b = 1.28$, $p = 0.01$; AN with abuse, $b = 1.40$, $p = 0.01$; BN without abuse, $b = 1.5$, $p < 0.001$), with the exception of BN with abuse (time effect, $b = 0.69$, $p = 0.16$). Only patients without abuse showed a reduction of SCL-90 global scores (time effects for AN without abuse, $b = 0.60$, $p = 0.01$; BN without abuse, $b = 0.54$, $p = 0.002$), while patients with abuse did not report any significant change (time effects for AN with abuse, $b = 0.001$, $p = 0.98$; BN with abuse, $b = 0.08$, $p = 0.88$). No significant correlation was detected between cortisol variation and EDE-Q or SCl-90 score reduction across time.

4. Discussion

As far as the first research hypothesis of the present study is concerned, patients affected by AN and BN reporting a history of childhood abuse reported lower basal cortisol levels with respect to AN and BN patients without early maltreatment and controls. In fact, as already described by other authors (Monteleone et al., 2015, 2018), we found that a history of childhood abuse could account for lower cortisol levels in AN and BN patients with respect to ED patients without exposure to early adversities. Only patients affected by AN without abuse showed higher cortisol levels. These findings are in line with a previous observation of Monteleone et al. (2015) that suggests that disease-induced malnutrition (associated with low BMI) and early maltreatment could have opposite effects on HPA-axis functioning. Moreover, a history of childhood abuse associated with HPA-axis hyporeactivity and relatively low cortisol levels has been broadly described in both nonclinical and clinical samples in several mental disorders (Bremner et al., 2003; Meinlschmidt and Heim, 2005; Elzinga et al., 2008; Mangold et al., 2010), with a remarkable HPA-axis hyporeactivity model in PTSD (Wessa et al., 2006). As far as the second research hypothesis of the present study is concerned, CBT determined a significant reduction of cortisol levels, and the effect of this cortisol reduction was reported in patients without a history of childhood abuse. The reduction of cortisol levels observed in patients without abuse is in line with previous studies reporting a similar reduction when using psychotherapy in patients with major depressive disorder (Yang et al., 2009), anxiety disorders (Brand et al., 2011; Rosnick et al., 2016) and PTSD (Bergen-Cico et al., 2014; Gerardi et al., 2010). Tafet et al. (2005) have observed a significant decrease in previously increased levels of circulating cortisol, along with a significant clinical improvement in response to CT in patients with generalized anxiety disorder. Tafet et al. (2005) have suggested that the positive effects produced by cognitive therapy could be understood as a significant improvement in the remodeling of underlying dysfunctional beliefs and the development of more effective strategies aimed at identifying and controlling worry, whose severity may be associated with increased cortisol levels (Chaudieu et al., 2008; Mantella et al., 2008). Moreover, the cognitive coping strategies learned through CBT have been shown to lower cortisol levels (Abelson et al., 2008). It can be hypothesized that the use of CBT—thanks to the remodeling of the dysfunctional beliefs of patients affected by AN and BN, the development of cognitive coping strategies and the ability of controlling worry—could ultimately decrease the psychological distress of patients and may determine cortisol reduction in patients without a history of childhood abuse. Finally, with regard to the third hypothesis, a different pattern of response to CBT in terms of cortisol changes has been observed in patients reporting a history of childhood abuse, namely the persistence of hypocortisolism from baseline to follow-up time after CBT in patients with childhood abuse. In the present study, a history of childhood abuse was found to be a moderator of cortisol variation after CBT. Indeed, only patients without abuse reported a reduction of cortisol levels, while patients with abuse did not report any significant change, with a flattened trajectory between the two time points. It can be hypothesized that early adverse experiences such as childhood abuse could have a long-lasting detrimental effect on HPA-axis functioning in EDs patients beyond the efficacy of the CBT treatment. As previously proposed by other authors (Binder and Holsboer, 2012), this specific result could be explained by a hyporeactivity of the HPA axis in subjects reporting early traumatic experiences. The underlying physiopathological mechanisms are still far from being completely elucidated, but according to Heim et al. (2008), early adverse experiences would lead to sensitization of central stress response systems with altered dynamics of the HPA axis. In particular, according to the allostatic theory (McEwen and Wingfield, 2003), a prolonged hyper-activation of the stress response systems, caused by repeated exposure to childhood abuse, may lead to long-lasting HPA-axis hypoactivity and/or hyporeactivity with low cortisol levels (Fries et al., 2005; Pryce et al., 2005). This phenomenon can be considered as a means of adaptation, in order to adjust the stress system's functioning to cope with the environmental demand and to avoid further damages deriving from high cortisol levels (Fries et al., 2005; Miller et al., 2007). Furthermore, trauma can determine modifications in brain structures and/or gene expression regulating the activity of the HPA axis with chronic effects on its responsiveness and functioning in adulthood (Houtepen et al., 2016; Lupien et al., 2009; Peckins et al., 2012). As already reported by Dahmen et al. (2018), exposure to early adversity has been associated with a smaller hippocampal volume and lower diurnal cortisol. It has been hypothesized that local neuronal damage and atrophy in the hippocampus could be due to an over-expression of stress hormones with elevated cortisol levels in acute phases of extreme adversity during childhood, and contribute to the development of hypocortisolism later in adulthood (Gunnar and Vazquez, 2001). Moreover, as far as the moderate role of childhood abuse in cortisol variation after CBT reported in our study is concerned, it is possible to hypothesize that a certain type of brain damage could be associated not only with the presence of hypocortisolism in AN and BN patients with a history of childhood abuse, but also with the persistence of this hypocortisolism after CBT. The results of the present study suggest possible clinical implications related to the management of patients with EDs reporting childhood abuse. Indeed, it is possible that CBT did not completely challenge some of the long-term psychopathological consequences of childhood abuse, as suggested by the persistence of a more severe general psychopathology (SCL-90) and a flattened trajectory with stable lower cortisol levels in abused patients after treatment. Therefore, this is a further confirmation of the need for the development of efficacious interventions to manage the long-lasting effects of childhood trauma, beyond the standardized CBT and pharmacological interventions for EDs. In conclusion, though preliminary, the results of the present study provide biological and clinical support for the maltreated ecophenotype theory, already suggested by Monteleone et al. (2018b). According to this approach, patients with a history of maltreatment and exposure to early adversities exhibit a more severe disorder and different biological characteristics compared to non-maltreated ones (Teicher and Samson, 2013).

The results of the present study should be considered in light of some limitations. The design of the study required several exclusion criteria, thus reducing the possibility to generalize the conclusion to all ED patients as well as yielding a relatively small sample size. Information on the history of abuse was assessed retrospectively, and could have been vulnerable to the recall biases inherent in this type of data. Adult trauma, which was considered potentially associated with HPA functioning by other authors, was not evaluated in this study. The main limitation was the sampling protocol of blood cortisol with one single measurement of cortisol in the morning. In fact, cortisol secretion follows a circadian rhythm throughout the day, and other parameters would have been more appropriate for investigating alterations in HPA axis activity (e.g., the cortisol awakening response, the diurnal slope or the total daytime cortisol output which can be retrieved from diurnal profiles of salivary cortisol which should be collected over at least two consecutive days) (Pruessner et al., 1997; Adam and Kumari 2009;

Hellhammer et al., 2007; Michopoulos et al., 2015)—especially for the studies with a longitudinal design and follow-up evaluation after 12 months, as it has been shown that cortisol is not very stable over such a long period of time (Skoluda et al., 2017). Moreover, the extreme methodological weakness of the one single blood cortisol measurement of this study may restrict the informative value and the reliability of the data as well as their interpretation. The results of the present study should be confirmed by means of studies with larger sample sizes, longer follow-up periods and more reliable and appropriate evaluation of HPA-axis functioning.

Conflicts of interest

None.

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