Alterations of the HPA Axis Observed in Patients with Major Depressive Disorder and Their Relation to Early Life Stress: A Systematic Review

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Keywords

Early life stress · Hypothalamic pituitary system · Major depressive disorder

Abstract

Background: Alterations of the hypothalamic-pituitary-adrenal (HPA) axis are common in patients diagnosed with major depressive disorder (MDD). Nevertheless, these alterations are not found in every patient. There is evidence to indicate a possible mediating role of early life stress (ELS) in the relation between dysfunction of the HPA axis and MDD. We conducted a systematic review to understand if the alterations of the HPA axis commonly found in patients with MDD are due to early life stress or are caused by the disorder itself. **Methods:** The review was conducted by following the PRISMA guidelines. Original articles were found in PubMed and via a manual search. Only studies whose design allowed comparison of the HPA functioning in the 4 groups no-MDD/no-ELS, MDD/no-ELS, no-MDD/ELS, and MDD/ELS were included. **Results:** Hyperactivity or hypoactivity of the HPA axis was found in 8 articles. A greater number of abnormalities and a higher rate of posttraumatic stress disorder comorbidity were found in the MDD/ELS group. Dysfunction of the

HPA axis was also found in the no-MDD/ELS groups. **Conclusion:** HPA dysfunction found in MDD seems to be more related to the presence of ELS rather than to the MDD itself. Future studies are needed to clarify the exact mechanisms involved.

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Introduction

Early life stress (ELS) is defined as having endured episodes of physical, psychological, and sexual abuse, or physical and emotional neglect, in addition to other traumatic events (including the loss of the main caregiver, prolonged hospitalization, invasive medical procedures, severe illness or trauma, natural disasters, etc.) during childhood. ELS has been linked to numerous physical and mental diseases [1–3], including major depressive disorder (MDD) [4–6].

Numerous morphological [7–9], endocrine [10, 11] and inflammatory [11] alterations have been found in patients with MDD. However, these findings are frequently inconsistent which is not surprising, considering the heterogeneity of the disease [12, 13]. Adults who suffer from

Fig. 1. Article selection flow diagram.

ELS often display disturbances of a similar nature [1, 14] whose causal mechanisms and relation to MDD are not fully understood [6, 10, 15, 16].

ELS is typically linked to worse physical and mental health outcomes in adulthood [17, 18]. Some authors have even postulated the existence of a new subtype of depressive mood disorder related to ELS [19, 20]. Patients diagnosed with MDD who have a history of ELS often present with symptomatology [21–23], chronicity [24–26], and a response to pharmacological and psychotherapeutic treatment [27–29] that differ from patients suffering from MDD only.

It is well known that stress triggers multiple physiological responses, perhaps the most representative being the activation of the hypothalamic-pituitary-adrenal (HPA) axis and its consequent release of adrenocorticotrophic hormone (ACTH) and cortisol. MDD has been traditionally associated with hyperactivity of the HPA axis [30], while posttraumatic stress disorder (PTSD), another related psychopathology, has been linked to a hypoactivity of the same axis [31]. Curiously, the co-occurrence of MDD and PTSD [32, 33] and a symptoms overlap is appreciable [34]. It has been postulated that ELS induces hypersecretion of corticotropin-release factor (CRF) by the hypothalamus [6] that results in a hyperactivity of the HPA axis and its consequent elevated cortisol release. This could ultimately lead to: (a) hypoactivity of the HPA axis due to an adaptative enhancement of negative feedback on

hypothalamic glucocorticoid receptors by cortisol, which could mirror biological malfunctions typically found in PTSD [31, 35]; (b) desensitization of CRF pituitary receptors caused by excessive CRF secretion, that could lead to a perpetuation of a high CRF concentration in the central nervous system (CNS); and (c) diminution of the number of or the desensitization of hypothalamic glucocorticoid receptors that results in an inhibition of the negative-feedback loop, and consequently permanent hyperactivity of the axis (elevated ACTH/cortisol secretion) [6, 10, 30].

This paper aims to elucidate the association of ELS and alterations of the HPA axis observed in patients diagnosed with MDD.

Methodology

This systematic review was conducted by searching in PubMed and a manual search approach in both English and Spanish in June 2019. Original articles were included without a time limit; any other type of article was excluded. To be able to analyze the relationship with alterations of the HPA axis, only studies whose design allowed comparison of the HPA functioning in the 4 groups, no-MDD/no-ELS, MDD/no-ELS, no-MDD/ELS and MDD/EL, were included.

PRISMA methodology [36] was used and the following MeSH terms were used: “child abuse,” “adult survi-

Table 1. The main characteristics from the selected articles

First author [ref.]	Year	Country	Participants, <i>n</i>	Test conducted	Sample	Summary
Newport [54]	2004	USA	64 women	DXM test (0.5 and 1 mg)	blood	hypoactivity of the HPA axis in ELS/MDD in response to DXM 0.5 mg, adequate response to DXM 1 mg basal hypoactivity of the HPA axis in ELS/no-MDD
Lu [37]	2016	China	80 women and men	salivary cortisol upon awakening and DXM test (1 mg)	saliva and blood	hypoactivity of the HPA axis in ELS/MDD in response to DXM, basal activity was normal salivary cortisol upon awakening was normal, but a greater increase of cortisol was found in the next hour in ELS groups
Heim [58]	2001	USA	66 women	CRF and ACTH ₁₋₂₄ stimulation test	blood	hypoactivity of the HPA axis found in ELS groups in response to CRF and ACTH ₁₋₂₄ stimulation
Suzuki [42]	2014	UK	80 women and men	stress reactivity test	saliva	hypoactivity of the HPA axis in ELS groups and hyperactivity in the no-ELS/MDD
Peng [62]	2014	China	109 women and men	–	saliva	hyperactivity of the HPA axis found in ELS/MDD vs. no-ELS/MDD and in ELS/no-MDD vs. no-ELS/MDD
Heim [51]	2008	USA	49 men	DXM/CRF test	blood	hyperactivity of the HPA axis found in the ELS/MDD group
Heim [60]	2000	USA	49 women	psychosocial stimulation test	blood	hyperactivity of the HPA axis found in ELS groups
Hinkelman [50]	2013	Germany	43 women and men	–	hair and saliva	hypoactivity of the HPA axis found in ELS groups

vors of child adverse events,” “child maltreatment,” “major depressive disorder,” and “mood disorder.” The article selection flow chart is shown in Figure 1. Initially, 1,397 results were obtained. After applying the free term “HPA axis,” the research was reduced to 34 articles. By manual search, 4 articles were found. After reading all of the abstracts, 10 articles were selected for full-text reading. Two articles were discarded due to not meeting 1 of the following inclusion criteria: (a) being published in Spanish or English; (b) reporting an evaluation of ELS on the activity of the HPA axis in patients with MDD (MDD/ELS and MDD/no-ELS groups) including a positive control for ELS (no-MDD/ELS) and a negative control (no-MDD/No-ELS). Ultimately, 8 articles were included. Table 1 summarizes the main characteristics of the selected articles.

Results

Cortisol levels are not homogenous throughout the day; they present a peak around 8:00 a.m. (maximum peak) and decrease until midday when another peak occurs. This is followed by another decrease of plasma cortisol, until the last peak which occurs before sunset. This

cortisol circadian rhythm is thought to be disrupted by chronic stress, ELS, and MDD. The regulation of the HPA axis is subjected to a negative-feedback loop where cortisol (secreted by the adrenal cortex) inhibits the release of CRF by the hypothalamus and ACTH by the pituitary gland. ACTH also inhibits CRF release.

The following were deployed by the different studies to measure the activity of the HPA axis. (a) basal cortisol and/or ACTH measurement in saliva usually during the early morning (upon awakening and minutes later) or hair cortisol/ACTH. (b) The dexamethasone (DXM) test, i.e., administering a dose of DXM (0.5 to 1.5 mg) at night (day 1) and measuring plasma cortisol the next morning (day 2). DXM is a synthetic glucocorticoid whose mechanism of action resembles that of endogenous cortisol. Therefore, a suppression of the HPA axis activity by the negative-feedback loop is expected upon its administration; patients with MDD are known to show abnormal responses to DXM [34]. That said, in normal circumstances, DXM suppresses ACTH and cortisol release. An abnormal suppression reaction, i.e., an excess (supersuppression) or reduced suppression, are signs of dysfunction of the HPA axis. Supersuppression occurs when the suppression is greater than that observed in healthy controls, while reduced suppression indicates a malfunction

Table 2. Detailed cortisol measurements and methods used in the different articles

First author [ref.], year	Measurement	cortisol CXM test				cortisol CRF test				cortisol ACTH ₁₋₂₄ test			
		ELS/ MDD	ELS/ no-MDD	no-ELS/ MDD	ELS/ no-MDD	ELS/ MDD	ELS/ no-MDD	ELS/ MDD	ELS/ no-MDD	ELS/ MDD	ELS/ no-MDD	ELS/ no-MDD	no-ELS/ MDD
Newport [54] ^p , 2004	= ^a ↓ ^a		= ^a		↓ ^{b,c,d,g}		=		=		=		
Lu [37], 2016	= ^{a,j,n} ↑ ^{a,j,o,g}		= ^{a,j,n} ↑ ^{a,j,o,g}		↑ ^{d,g}		=		=		=		
Heim [58], 2001	↓ ^a		= ^a		-		↓		↓		=	↓	=
Suzuki [42] ^j , 2014	= ^{a,j,g,i,q}		= ^{a,j,g,i,q}		↑ ^{a,d,h} ↑ ^{i,d,h}		-		-		-	-	-
Peng [62], 2014	= ^k		= ^k		↓ ^{d,h}		-		-		-	-	-
Heim [51], 2008	-		-		=		=		↑ ^{g,l}		=	-	-
Heim [60], 2000	↑ ^{i,g,d}		↑ ⁱ		-		-		-		-	-	-
Hinkelmann [50], 2013	↓ ^{g,i,m}		↓ ^{g,i,m}		-		-		-		-	-	-

↑ greater than the control; ↓ smaller than the control; = no significant difference; - no data.
^a Basal levels (without pharmacological and psychosocial stimulation); ^b plasma level at 8:00; ^c plasma ratio 8:00/basal; ^d same difference found when compared to the ELS/no-MDD group; ^e plasma level at 16:00; ^f plasma ratio 16:00/basal; ^g same difference found when compared to the no-ELS/MDD group; ^h same difference found when compared to the ELS/no-MDD group; ⁱ stress reactivity to psychosocial stress; ^j salivary cortisol; ^k significantly higher than no-ELS/MDD; ^l DXM/CRF test after the administration of CRF; ^m same results in hair cortisol; ⁿ cortisol levels upon awakening; ^o cortisol levels 1 h after awakening; ^p result of the low-dose DXM stimulation test (0.5 mg) but no difference was found with 1 mg DXM; ^q considered by the author.

of the negative autoregulatory feedback loop. (c) The CRF test, whereby multiple blood samples are extracted at different times to quantify ACTH and cortisol variations following the administration of 1 µg/kg of ovine CRF. (d) The ACTH₁₋₂₄ test, i.e., 250 µg of synthetic ACTH₁₋₂₄ is administered and, during the subsequent hours, multiple plasma cortisol samples are analyzed to quantify cortisol. Both the CRF and ACTH tests measure an immediate response but not the ability to regulate the HPA axis. A stimulation of cortisol secretion is expected in both tests, since synthetic CRF mimics endogenous CRF (released by the hypothalamus) that binds to CRF receptors at the pituitary gland and stimulates the secretion of ACTH. ACTH binds to ACTH receptors in the adrenal cortex which stimulates the production of cortisol. (e) The DXM/CRF test. The DXM test is performed as previously described and then at midday the next day, 100 µg of CRF is administered following the extraction of the last blood sample for the DXM test. Plasma cortisol and ACTH are measured again. The cortisol and ACTH secretory responses to CRF should be suppressed by the previous administration of DXM. Higher plasma cortisol than normal after the administration of the CRF indicates an inability to suppress the HPA axis, considering the previous administration of DXM and a probable lack of sensitivity of the hypothalamic glucocorticoid receptors that are part of the negative-feedback loop; this could be caused by a past or present state of hypercortisolemia. (f) The stress reactivity test: participants are exposed to stressful situations and blood samples are taken to evaluate the HPA axis response to stress. (g) The Trier social stress test, whereby participants are asked to perform different activities in public, and blood samples are taken to examine their HPA axis response to social stress.

Details of the measurements performed in each article are presented in Table 2 (cortisol) and Table 3 (ACTH).

The principal tests for evaluating the magnitude of ELS are the Childhood Trauma Questionnaire (CTQ) and the Early Trauma Inventory (ETI). The CTQ is a self-report questionnaire that covers 28 items and evaluates the presence and severity of emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, and the possibility of denial. The ETI is also a self-report questionnaire that is divided into 5 sections: general trauma (involvement in serious accidents, severe illness or death of caregivers, parents' divorce, etc.); physical punishment (physical abuse); emotional abuse; sexual abuse; and emotional response at the time of the events. In both tests, the events considered must have occurred before the age of 18 years.

Table 3. Detailed ACTH measurements and methods used in the different articles

First author [ref.], year	ACTH measurement								
	ACTH			ACTH DXM test			ACTH CRF test		
	ELS/ MDD	ELS/ no-MDD	no-ELS/ MDD	ELS/ MDD	ELS/ no-MDD	no-ELS/ MDD	ELS/ MDD	ELS/ no-MDD	no-ELS/ MDD
Newport [54], 2004	=	=	=	= ^a ↓ ^{b, c} = ^c ↓ ^d	=	=	–	–	–
Lu [37], 2016	–	–	–	–	–	–	–	–	–
Heim [58], 2001	–	–	–	–	–	–	↓	↑	↓
Suzuki [42], 2014	–	–	–	–	–	–	–	–	–
Peng [62], 2014	–	–	–	–	–	–	–	–	–
Heim [51], 2008	–	–	–	↑ ^e	–	–	↑ ^e	–	–
Heim [60], 2000	↑ ^{h, e}	↑ ^h	=	–	–	–	–	–	–
Hinkelman [50], 2013	–	–	–	–	–	–	–	–	–

↑ greater than the control; ↓ smaller than the control; = no significant difference; – no data.

^a Plasmatic levels at 8:00. ^b Same difference found when compared to the ELS/no-MDD group. ^c Plasma level at 16:00. ^d Plasma ratio 16:00/basal.

^e Same difference found when compared to the no-ELS/MDD group. ^h Stress reactivity to psychosocial stress.

General and Unspecified Abuse

Lu et al. [37] conducted a study on 80 subjects in China aged between 18 and 45 years. Eighteen subjects met the criteria to be diagnosed with MDD and suffered from ELS (MDD/ELS group), 17 subjects met the criteria for MDD without ELS (MDD/no-ELS), 23 were healthy controls that suffered from ELS (no-MDD/no-ELS), and the remaining 22 were free from MDD and ELS (no-MDD/no-ELS). Exclusion criteria were: diagnosis of another axis I/II psychiatric disorder (excluding MDD), substance abuse (including alcohol), or a family history of bipolar disorder. Women who were pregnant, breastfeeding, had their menstrual period or were on hormonal treatment were also excluded.

ELS was evaluated using the CTQ [38]. No significant difference was observed between the MDD/no-ELS and no-MDD/no-ELS groups for any subscale of the CTQ. The MDD/ELS group scored higher than the MDD/no-ELS and no-MDD/no-ELS for all subscales apart from sexual abuse, where no difference was observed. It is interesting to note that the MDD/ELS group scored higher than the no-MDD/ELS group only on the emotional abuse subscale and total score, which could indicate a special role of emotional abuse in the development of MDD in adulthood. MDD diagnosis was assessed with the Structured Clinical Interview for DSM-IV (SCID) [39],

and the severity of depression was assessed with the Hamilton Depression Scale (HAM-D)-24 [40] and Self-Rating Depression Scale (SDS) of Zung et al. [41]. Salivary cortisol samples were collected upon awakening and after the next 30, 45, and 60 min. A DXM test was also performed. Salivary cortisol concentration at all times was higher in the ELS group with and without MDD compared to those subjects without ELS. Moreover, a correlation between the CTQ punctuation and awakening salivary cortisol was found. The 4 groups showed similar plasma cortisol levels before the DXM administration. Interestingly, the ELS/MDD group response to DXM was minimal; patients with ELS and MDD released much more cortisol post-DXM and the suppression ratio was particularly low in this group whereas the no-ELS/MDD group showed normal values.

Suzuki et al. [42] evaluated the reactivity to stress in 80 subjects: 17 healthy subjects with ELS/no-MDD, 24 healthy subjects with no-ELS/no-MDD, 21 patients with ELS/MDD, and 18 no-ELS/MDD patients. ELS was assessed using the CTQ [38]. The ELS groups scored higher than the no-ELS groups on all subscales, scoring particularly noticeably higher on the emotional abuse and emotional neglect subscales. MDD diagnosis was made following the ICD-10 criteria and depressive symptomatology was evaluated with the Quick Inventory of Depressive

Symptomatology Self-Report (QIDS-SR) [43]. Stress reactivity was performed by showing different images to the participants at 2 sessions. During the first session participants merely observed, while during the second session they were asked to classify the images depending on the feelings these evoked. Seventy-two images from the International Affective Picture System were used (24 positives, 24 neutral, and 24 negatives) [44]. Cortisol samples were obtained before and after each session. After both sessions, the following tests were performed: the Zung anxiety scale [45], the Rosenberg self-esteem scale [46], the social readjustment rating scale [47], the impact of events scale [48], and the dissociative experience scale [49]. Averaged cortisol was higher in the MDD groups than in the no-MDD groups. Those with no-ELS/MDD showed higher cortisol secretion than the ELS/MDD group. The greater cortisol response found in MDD groups was due to the levels found in the no-ELS/MDD group, since the ELS/MDD and ELS/no-MDD groups showed no significant difference.

Hinkelman et al. [50] conducted a study to determine differences in the hair and salivary cortisol of subjects with ELS with and without depression; 43 people (27 women and 16 men) with an average age of 41.7 years were evaluated. All of them were diagnosed with MDD according to the DSM-IV criteria, and a minimum punctuation of 18 on the HAMD [40] was required. Twenty-four of those diagnosed with MDD were considered CTQ+ (ELS) after the CTQ [38] was applied, and the remaining 19 were considered CTQ- (no-ELS). Scoring high for only 1 of the different types of trauma was considered enough to be included in the CTQ+ (ELS) group. As a control group, 26 women and 15 men matched by age free of any axis I/II disorder were selected, and 7 were then considered CTQ+ (ELS). The ELS group had lower cortisol levels in the hair and saliva than the no-ELS group. Moreover, a greater concentration of cortisol was correlated with a lower punctuation on the CTQ, suggesting a relation between ELS and cortisol release. When the ELS group was divided depending on the MDD diagnosis, it was observed that MDD did not influence cortisol levels. Antidepressant treatments, smoking, and atypical depression did not seem to influence cortisol levels, indicating that ELS may have the greater influence.

Physical and Sexual Abuse

Heim et al. [51] evaluated cortisol and ACTH response to the DXM/CRF test in 49 males aged between 18 and 60 years. Of these, 14 were in the group no-ELS/no-MDD, another 14 were in the group ELS/no-MDD, 13 were in

the group ELS/MDD, and the remaining 6 were diagnosed with MDD but did not suffer from significant ELS (no-ELS/MDD). A psychiatric assessment was done with the SCID [39] and ELS was evaluated with the ETI [52]. Subjects in the ELS groups had to have endured significant physical or sexual abuse before the age of 13 years. The ELS groups scored much higher than the no-ELS groups on all subscales, with the highest scores being for physical and emotional abuse. Depressive symptoms were assessed with HAMD-21 [40]; and posttraumatic stress symptoms with the Clinician-Administered PTSD Scale (CAPS) [53]. Regardless of the presence of MDD, patients with ELS released more cortisol. Plasma ACTH was also higher in the ELS groups. Those with ELS were further divided into 2 groups depending on the presence of PTSD symptoms (ELS/PTSD and ELS/no-PTSD); ACTH concentration was far lower in the ELS/PTSD group. No difference was found concerning cortisol.

Newport et al. [54] measured the cortisol response to the DXM suppression test at the usual dose (1 mg) and a low dose (0.5 mg) in 64 women; 19 were healthy (no-ELS/no-MDD), 19 were suffering from ELS but not depression (ELS/no-MDD), 16 had both (ELS/MDD), and the remaining 10 had MDD but no history of ELS (no-ELS/MDD). The prevalence of ELS was evaluated with the ETI [52] and recent traumatic events were evaluated with the Life Experiences Survey (LES) [55] and Perceived Stress Scale (PSS) [56]. All ELS subjects had to have endured significant physical or sexual abuse before their first menstrual period. No significant difference between the ELS/MDD and ELS/no-MDD groups was observed for the total ETI score. A psychiatric evaluation was performed using the SCID [39], and depression and anxiety severity were assessed with the HAMD [40] and Hamilton Anxiety Scale (HAMA) [57], respectively. Ninety-four percent of patients in the ELS/MDD group also met the criteria for PTSD, while only 26% of patients in the ELS/no-PTSD group met these criteria. No difference was found in the DXM test at the regular dose. At a low dose, differences were found between the control (no-ELS/no-MDD) and ELS/MDD groups. The suppression ratio, i.e., $ACTH_{4\text{ p.m.}/\text{basal}}$ of the ELS/MDD group was significantly lower than in the control group (no-ELS/no-MDD). ELS/no-MDD group basal cortisol was also much lower than in controls. At 8 a.m., after the DXM suppression test (cortisol post-DXM), ELS/MDD cortisol concentration was significantly lower than in controls. The ratio $cortisol_{8\text{ a.m.}/\text{basal}}$ was found to be far lower in the ELS/MDD group than in the control and ELS/no-MDD groups. Patients without MDD, regardless of the presence of a his-

tory of ELS, showed a similar suppression ratio. The ratio cortisol_{4 p.m./basal} was significantly lower than in controls only in the ELS/MDD group; this points to greater suppression by DXM of HPA axis activity in patients with both ELS and MDD.

The prevalence of supersuppression was as follows: 93.8% in the ELS/MDD group, 68.4% in the ELS/no-MDD group, 50% in the no-ELS/MDD group, and 36.6% in the control group (no-ELS/no-MDD). When the PTSD diagnosis was considered, it became evident that the ELS/PTSD group had far lower post-DXM ACTH levels than the ELS/no-PTSD group; 90% of ELS/PTSD subjects were classified as supersuppressors, while only 66.7% of ELS/no-PTSD subjects and 64.3% of ELS/no-PTSD/no-MDD subjects were supersuppressors.

Heim et al. [58] evaluated 66 women, 20 of them with no significant history of ELS and mental disorders (no-ELS/no-MDD), 20 with ELS but without MDD (ELS/no-MDD), 15 without ELS and with MDD (no-ELS/MDD), and 11 with ELS and MDD (ELS/MDD). Basal cortisol and ACTH were measured from 13:30 to 16:00 at 30-min intervals. Two tests were performed: CRF and ACTH_{1–24 h} stimulation. MDD and other diagnoses were assessed with the SCID [39] and ELS was evaluated with the ETI [52], LES [55], and the “Daily Hassles Scale” [59]. All ELS group subjects had to have endured significant physical or sexual abuse before their first menstrual period. No significant difference between the ELS/MDD and ELS/no-MDD groups was observed for the total ETI score; 93.3% of women with ELS/MDD but only 20% of women with ELS/no-MDD met the criteria for PTSD. The high incidence of PTSD comorbidity could be due to including only women who had endured physical and/or sexual abuse at a young age in the ELS groups. During the CRF test, ELS/no-MDD subjects showed greater ACTH release than controls (no-ELS/no-MDD), while women with MDD showed decreased ACTH concentration regardless of the presence of ELS. With respect to plasma cortisol, women with ELS (with or without MDD) released less cortisol. During the ACTH stimulation test, the same results were observed regarding cortisol in women with ELS with and without MDD.

Heim et al. [60] also evaluated stress reactivity in 49 women (aged 18–45 years) using the Trier Social Stress Test [61]. The women were divided into 4 groups: 12 no-ELS/no-MDD, 14 ELS/no-MDD, 13 ELS/MDD, and 10 no-ELS/MDD. ELS was evaluated with the ETI [42], psychiatric disorders with the SCID [39], and depressive symptomatology with the HAMD [40]. All ELS group subjects had to have endured significant physical or sex-

ual abuse before their first menstrual period. No significant difference between the ELS/MDD and ELS/no-MDD groups was observed on the sexual and physical abuse subscales. Five ELS/no-MDD patients ($N = 14$) and 11 ELS/MDD patients ($N = 13$) met the criteria for PTSD. Blood samples were taken 15 min before the test, 15 min after beginning the test, and 30, 45, 60, 75, and 90 min after finishing the test. Regardless of the MDD diagnosis, the ELS groups showed a greater ACTH increase than the no-ELS groups did. Women with ELS/MDD showed a greater cortisol increase than the other 3 groups, but the no-ELS/MDD group did not show an abnormal response.

Physical and Emotional Neglect

Peng et al. [62] measured salivary cortisol upon awakening, with the intention of relating it to dysfunctional attitudes during episodes of MDD. They divided 109 participants into 4 groups: 28 ELS/MDD, 30 no-ELS/MDD, 22 ELS/no-MDD, and 29 no-ELS/no-MDD. Salivary cortisol was measured upon awakening and 30 min later. The occurrence of adverse events during childhood as well as their type and severity were evaluated with CTQ [38], depression was assessed with the SCID [39], depressive symptoms with the HAMD [40], and dysfunctional attitudes with the Dysfunctional Attitudes Scale (DAS) [63]. Only physical and emotional neglect were considered; all other types of childhood trauma were excluded. Moreover, social support was evaluated with the Suicide Severity Rating Scale (SSRS) [64]. Patients with ELS/MDD showed greater HPA axis abnormalities than no-ELS/MDD patients. Patients with a history of negligence but without depression (ELS/no-MDD) also showed more abnormalities than no-ELS/no-MDD patients.

Negligence during childhood was related to dysfunctional attitudes but it was not associated with depression severity according to the HAMD. However, dysfunctional attitudes in the no-ELS/MDD group were not significantly different from the ELS/no-MDD group, suggesting that negligence during childhood, whether or not depression manifests in adulthood, results in dysfunctional attitudes similar to those of depressed patients.

Discussion

HPA axis anomalies were found in all articles included in our review but were not consistent, either in their nature or between groups. It seems that ELS disturbs the activation of the HPA axis. Nevertheless, the nature of the alteration depends on the stress but potentially also on

other activity, e.g., the mediation effect of depressive symptomatology and alterations in epigenetic regulatory mechanisms [65].

In the studies conducted by Lu et al. [37], Newport et al. [54], and Heim et al. [51, 58], the response of the HPA axis to different active pharmaceutical ingredients or/and hormones was assessed (DXM, CRF, and ACTH₁₋₂₄). Higher cortisol secretion was found among those with a history of ELS regardless of MDD status. Decreased suppression of the HPA axis following the administration of DXM was found only in ELS/MDD patients. Interestingly, no HPA axis anomalies were found in the no-ELS/MDD patients, suggesting that anomalies found in patients with MDD are not caused by MDD itself but by the comorbid presence of ELS. The aforementioned stress would be a trigger for hyperactivity of the HPA axis which, in turn, can make an individual vulnerable to the development of MDD and other disorders [3, 6, 66]. HPA axis anomalies may precede the MDD, so ELS may be a cause or a risk factor for MDD rather than a consequence or a symptom. The development of MDD can accentuate HPA dysfunction. The symptoms of MDD (insomnia, reduction of physical activity, poor eating habits, etc.) can worsen the HPA axis malfunction and/or adversely affect its regulation.

Other authors have considered the presence or absence of PTSD along with MDD. Sufferers of PTSD and ELS have a higher ACTH plasmatic concentration than those without PTSD. These results are in agreement with previous PTSD findings [31, 67], and possibly explain the seemingly paradoxical observations made by Newport et al. [54] (i.e., hypoactivity of the HPA axis in MDD) versus what Lu et al. [37] and Heim et al. [51] found (i.e., hyperactivity of the HPA axis in MDD). This discrepancy could also be partially explained by variations in inclusion criteria with regard to the type of trauma and gender. Heim et al. [51] included only males who suffered from physical and/or sexual abuse in the ELS groups. Newport et al. [54] included only women with the same childhood trauma. Lu et al. [37] included both men and women with all types of ELS. Considering the overlap between different types of abuse and the frequent lack of difference in CTQ/ETI scores between the ELS/MDD and ELS/no-MDD groups, it is difficult to determine a clear relationship between types of abuse and HPA axis alterations.

Newport et al. [54] observed that those individuals who had suffered from ELS and were diagnosed with MDD presented with a hypoactivity of the HPA axis when compared with controls (no-MDD/no-ELS). However, those who suffered from ELS but did not meet the criteria for MDD showed hyperactivity of the HPA axis

in response to DXM, similar to the response in controls. This discrepancy could possibly be explained by the fact that 94% of the MDD/ELS group also met the criteria for PTSD, while only 26% of the no-MDD/ELS group were diagnosed as having PTSD. This would point to the hyperactivity of the HPA axis being mainly associated with the PTSD, which allows a distinction to be made between ELS/MDD/PTSD and ELS/MDD/no-PTSD, reinforcing the hypothesis that MDD/PTSD comorbidity represents a more differentiated MDD subtype [68], a posttraumatic mood disorder [20], or a different endophenotype of the illness.

Other authors have defined a subtype of MDD associated with anxiety symptomatology; this is characterized by a worse prognosis, more severe depression, and more alterations of the HPA axis. In this subtype, the incidence of ELS is much higher [69].

To understand the relationship of anxiety disorder, depressive disorder, and ELS, it would be interesting to develop research lines that allow the distinguishing of the effects of PTSD, other anxiety disorders, and MDD in individuals who suffer from ELS as well as a comparison with healthy subjects.

Heim et al. [58] observed that women who suffered abuse during childhood showed a decreased cortisol release in response to the ACTH₁₋₂₄ test. On the one hand, these results are coherent with the hypothesis of a hypoactivation of the HPA axis following an initial state of hyperactivity [67], and, taking the high comorbidity with PTSD in the ELS/MDD group, it is also coherent with the idea of MDD/PTSD comorbidity representing a different nosological entity [68]. On the other hand, the women suffering from ELS who did not meet the criteria for MDD (ELS/no-MDD) showed an increased secretion of ACTH during the CRF test compared with MDD/ELS women. This reinforces the hypothesis of a desensitization of pituitary CRF receptors, caused by excessive release of CRF, being an important factor in the development of MDD [6].

Regarding stress reactivity, Suzuki et al. [42] found that ELS sufferers release less cortisol when subjected to the test. These results are coherent with the notion of hypoactivity of the HPA axis following hyperactivity [67]. However, the lack of standardization of images and the possibility that those who suffer from ELS are simply more used to ungradable visual stimuli made it difficult to replicate these results. In contrast, Heim et al. [60] used a standardized method to study reactivity to stress and found greater reactivity in ACTH and cortisol measurements in ELS sufferers. It is interesting to point out that

no-ELS/MDD subjects show a greater reactivity to stress, supporting the hypothesis that the traditionally observed HPA axis anomalies in patients with MDD are not due to the depressive disorder itself but to the comorbid ELS [4, 10]. Similar results were obtained when studying HPA axis activity and the influence of ELS in other disorders such as borderline personality disorder [70]. Greater punctuation in the ETI, a sign of greater ELS, was related to elevated plasmatic cortisol and ACTH concentration, except in those who also had PTSD.

Peng et al. [62] found a relationship between negligence and dysfunctional attitudes and increased HPA axis dysfunction in ELS/no-MDD groups when compared to no-ELS/no-MDD groups. This could increase an individual's vulnerability to developing MDD. More studies are needed to understand if negligence could be indirectly related to MDD through learnt behaviors (dysfunctional attitudes) or if the negligence per se causes a disruption of the HPA axis.

Hair cortisol analysis is known to provide a more precise image of long-term cortisol secretion [50]. It would potentially be useful to verify if a transition from a hyperactivity to a hypoactivity of the HPA axis actually occurs. In this review, we found that cortisol levels were lower in patients with ELS. Hair cortisol measurement could elucidate the impact that the age at which the trauma happened and the length of time since the event have on the nature and severity of the HPA axis alteration.

Limitations of the Study

A direct comparison between studies turned out to be difficult on account of the lack of agreement on the following aspects: (a) the age considered as "childhood": the younger the individual is, the greater their vulnerability

to stress, i.e., stress could lead to different consequences depending on the developmental stage of the individual when it occurs; (b) the type of stressful event; (c) the different scales and tests used for the evaluation; and (d) the different methods to evaluate the activity of the HPA axis.

To summarize, in order to clarify and deeply understand the implications of ELS on the HPA axis, it is imperative to track the activity of the HPA axis (by means of cohort studies) and be in consensus about the method for evaluating HPA axis function. This will enable a direct comparison between studies and distinguish between subjects diagnosed with MDD, PTSD, or both. This is necessary to appropriately evaluate the activity/malfunction of the HPA axis in each case, and, if applicable (as proposed by some authors), consider the existence of an independent nosological entity (a comorbid MDD/PTSD endophenotype) and the factors contributing to its development.

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Author Contributions

A.C. conducted the articles search for this review under the supervision of Monica M.-C. A.C. and Monica M.-C. extracted the relevant information from each paper reviewed. Mayte M.-C. and A.P.-C. worked in the interpretations of the extracted data. A.C. wrote the main manuscript and all authors reviewed and approved it.

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