World Journal of Psychiatry

Online Submissions: http://www.wjgnet.com/esps/
wjp@wjgnet.com
doi:10.5498/wjp.v2.i1.13

World J Psychiatr 2012 February 22; 2(1): 13-25
ISSN 2220-3206 (online)

REVIEW

Childhood stressful events, HPA axis and anxiety disorders

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Received: September 6, 2011 Revised: October 24, 2011
Accepted: January 21, 2012
Published online: February 22, 2012

Abstract

Anxiety disorders are among the most common of all mental disorders and their pathogenesis is a major topic in psychiatry, both for prevention and treatment. Early stressful life events and alterations of hypothalamic pituitary adrenal (HPA) axis function seem to have a significant role in the onset of anxiety. Existing data appear to support the mediating effect of the HPA axis between childhood traumata and post-traumatic stress disorder. Findings on the HPA axis activity at baseline and after stimuli in panic disordered patients are inconclusive, even if stressful life events may have a triggering function in the development of this disorder. Data on the relationship between stress, HPA axis functioning and obsessive-compulsive disorder (OCD) are scarce and discordant, but an increased activity of the HPA axis is reported in OCD patients. Moreover, normal basal cortisol levels and hyper-responsiveness of the adrenal cortex during a psychosocial stressor are observed in social phobics. Finally, abnormal HPA axis activity has also been observed in generalized anxiety disordered patients. While several hypothesis have attempted to explain these findings over time, currently the most widely accepted theory is that early stressful life events may provoke alterations of the stress response and thus of the HPA axis, that can endure during adulthood, predisposing individuals to develop psychopathology. All theories are reviewed and the authors conclude that childhood life events and HPA abnormalities may be specifically and trans-nosographically related to all anxiety disorders, as well as, more broadly, to all psychiatric disorders.

Key words: Anxiety disorders; Early stressful life events; Childhood traumata; Cortisol; Hypothalamic pituitary adrenal axis; Vulnerability; Psychopathology

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Faravelli C, Lo Sauro C, Godini L, Lelli L, Benni L, Pietrini F, Lazzeretti L, Talamba GA, Fioravanti G, Ricca V. Childhood stressful events, HPA axis and anxiety disorders. *World J Psychiatr* 2012; 2(1): 13-25 Available from: URL: http://www.wjgnet.com/2220-3206/full/v2/i1/13.htm DOI: http://dx.doi.org/10.5498/wjp.v2.i1.13

INTRODUCTION

Anxiety disorders are among the most common of all mental disorders[1]. The diagnostic and statistical manual of mental disorders (DSM-IV-TR)[2] includes generalized anxiety disorder (GAD; a chronic form of anxiety characterized by excessive, uncontrollable worry), panic disorder (PD; with recurrent, unexpected paroxysms of anxiety, somatic and autonomic symptoms and fear), phobic disorders [e.g., specific phobias, agoraphobia, so-

cial phobia (SP)], posttraumatic stress disorder (PTSD; characterized by unwanted, intrusive remembrances - as daytime thoughts and night-time dreams and nightmares - and avoidance of activities and other cues associated with prior life-threatening trauma) and obsessive-compulsive disorder (OCD; with recurrent obsessions and compulsions) in this category.

Exposure to stressors (i.e., early stressful life events) and sensitivity to stress have been strongly implicated in the manifestation or exacerbation of these syndromes[3-11]. Accordingly, the available literature reports that adults with an history of adverse childhood experiences develop anxiety disorders more frequently than adults without early stress[3-5,12].

However, studies about early life stress have investigated different periods of childhood and different adverse experiences. In the present review, the authors will consider the following early stressful life events, or adverse experiences: parental neglect; physical, emotional and sexual abuse; separation or death of a parent; and living with a mentally ill parent likely to be unable to provide continuous parental care. Frequency and duration of abuse, abuse involving penetration, force or violence, and a close relationship to the perpetrator, as well as early parental loss, appear to be the most harmful factors in terms of long-lasting effects on the child[4,6,7,10]. Usually, stressful events will be considered traumatic when they involve actual or threatened death or serious injury to oneself, or another threat to one's physical integrity, to which the subjects respond with intense fear, helplessness or horror (or in children, the response must involve disorganized or agitated behavior)[2].

Preclinical studies in animals and humans suggest that an early-life stressor (e.g., maternal separation during infancy, childhood abuse and neglect) is associated with marked long-term changes in brain circuitry regulating stress reactivity, mood and behavior (e.g., corticotropin releasing factor-containing neurons)[3].

Several clinical models suggest that early stressful life events may provoke dysfunctions in the central nervous system[13] and alterations of the stress response that can endure during adulthood[14-16]. In fact, physical and psychological stress experiences activate the hypothalamic pituitary adrenal (HPA) axis[17] through the secretion of corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) by the parvocellular neurons of the paraventricular nucleus of the hypothalamus. These neuropeptides activate the synthesis and the release of adrenocorticotropin hormone (ACTH) from the anterior pituitary, which successively stimulates the adrenal cortex to synthesize glucocorticoids, i.e., cortisol in humans. Cortisol influences several physiological processes and the synthesis of neurotrophic factors, with effects on mood and behavior[18,19].

Several methods evaluate HPA axis functioning through dosage of cortisol in a 24 h urine collection, in plasma/serum, in saliva or in cerebrospinal fluid (CSF), both in a basal condition and after stimuli. The main difference between these dosages is that less than 10% of plasmatic cortisol is free and thus biologically active, whereas salivary and urinary cortisol consists completely of the free (bioactive) fraction. On the other hand, the majority of plasmatic cortisol is bound to cortisol-binding globulin or to other proteins and is biologically inactive. As plasma free cortisol is in equilibrium with salivary cortisol, the latter is preferred as it is an easily obtainable biofluid and noninvasive source for evaluating the HPA axis.

Moreover, since cortisol has a circadian rhythm, with low values at awakening, followed by peak values 30 min after awakening and a steady decline during the rest of the day, several measures across the day explore HPA axis activity and the efficacy of the physiological evening downregulation.

Several stress tests can be applied: the most widely used method is the dexamethasone (Dex) suppression test (DST), which explores HPA axis functioning by measuring the suppression of cortisol levels induced by the administration of Dex; the Dex suppression CRH stimulation test (Dex/CRH test) explores pituitary and adrenal functioning by measuring ACTH and cortisol levels after a low-DST and subsequent stimulation with CRH; the combined administration of CRH and AVP (CRH/AVP test) helps investigate the activity of the HPA axis by measuring both the response of cortisol (adrenal) and ACTH (pituitary) to a stressor; and the ACTH stimulation test explores adrenal activity by measuring cortisol levels.

The relationship between stress, HPA axis hormones and psychopathology has been demonstrated in animal and human models.

Studies on rodents have shown that early social isolation provokes behavioral abnormalities similar to human depression and anxiety disorders, while environmental enrichment displays an antidepressive and anxiolytic effect in animal models of depression and anxiety[20].

Increased plasmatic ACTH and cortisol levels have been observed during behavioral despair in neonate non-human primates when separated from the mother[21,22].

Furthermore, when CRH is injected into the cerebral nervous system of laboratory animals, it produces effects reminiscent of stress, depression, fear and anxiety through actions on specific brain regions[4,23-25].

Breier *et al*[14] observed 90 subjects exposed to early parental loss in childhood and found higher plasma cortisol and ACTH concentrations in subjects who had obtained a lifetime psychiatric diagnosis, compared to those who did not receive a psychiatric diagnosis.

More recently, some authors observed that children who experienced permanent or long-term separations from parents, or parental death, show a hyperactive HPA axis, with increased basal salivary cortisol concentrations[26,27] and cortisol non-suppression after the DST[28], as well as the combined Dex/CRH test[29].

Moreover, alterations of the HPA axis have been

widely reported in psychiatric disorders, including anxiety disorders[30-39]. For instance, Vreeburg *et al*[40] showed a modest but significantly higher 1 h cortisol awakening response among anxious patients, especially in those with PD with agoraphobia and those with comorbid depression. However, if the diagnosis of current anxiety disorder was associated with higher awakening cortisol levels, remitted anxiety only showed a trend toward higher morning cortisol and any association was observed between anxious status and evening cortisol level or cortisol suppression after Dex administration[40].

However, neither the excess of stressful events during childhood nor the abnormalities of the HPA axis seem to be specific to any diagnostic group[11,41,42]. Moreover, data concerning the HPA axis in all anxiety diagnostic subgroups are scarce and few studies have examined the role of the HPA axis as a mediating factor between childhood stressful life events and anxiety disorders[3,4,11].

The present paper aims at reviewing the data on HPA axis functioning in anxiety disorders and the relationship between childhood stressful life events and these neuroendocrine alterations. Moreover, a hypothesis attempting to explain these associations will be discussed.

CHILDHOOD STRESSFUL EVENTS, HPA AXIS AND PTSD

PTSD is a chronic psychiatric condition that may develop in subjects who have been exposed to or have witnessed an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others, experiencing fear, helplessness or horror[2]. This psychiatric condition is frequent in subjects with a history of adverse childhood experiences[4,12,43-45].

Data about HPA axis functioning and its relationship with early life stress in PTSD are reported in Table 1.

Preclinical evidence showed a long-term sensitization of the stress response after early life stress[14]. Other authors reported increased cortisol levels in women with PTSD who experienced a childhood abuse[46,47] and in prepubertal children with PTSD secondary to past childhood maltreatment experiences[48], compared to non traumatized subjects.

Recent studies have provided evidence for sustained increases in CRH activation in the CSF of PTSD patients[49-51].

According to these findings, even in anticipation of and during a stressful cognitive challenge, PTSD patients with childhood abuse showed higher mean cortisol levels compared to healthy subjects[52-54]. Moreover, after CRH and ACTH administration, PTSD patients with childhood trauma had greater ACTH and cortisol responses, as well as a later cortisol peak[55,56].

On the other hand, Santa Ana *et al*[57] found that adults with PTSD had a less robust ACTH response to a cold pressor task compared to controls, regardless of age of index trauma. Moreover, when trauma happened in childhood, cortisol at baseline and at all post-task measurements was lower and did not display the decrease in cortisol over the course of the 2 h monitoring period, which was observed in subjects with adult index trauma and controls.

Similarly, after a CRH stimulation test, De Bellis *et al*[58] and Bremner *et al*[54] reported that childhood abused women with PTSD exhibited a significantly smaller ACTH response and no difference in cortisol response, than the healthy control group. Moreover, an excessive suppression of cortisol in response to a low dose of Dex (0.5 mg) was reported in similar groups of patients, compared to controls[31,59-61].

In contrast, other studies found no difference between women with PTSD and healthy subjects in terms of circadian rhythm of cortisol, baseline cortisol and ACTH levels[56,62] and in cortisol levels after DST[47].

In summary, these data show high baseline CRH levels and low plasma cortisol levels in PTSD patients and seem to confirm the mediating effect of the HPA axis between childhood traumata and PTSD[14,55,63].

A possible explanation for this finding is that high cortisol levels reflect an initial sensitization to the persistent intrusive nature of the memories and the continued sense of threat experienced by these individuals[64], while the following blunted response may reflect a physiological adaptation of the HPA axis to chronic stress, with the downregulation of the pituitary CRH-receptors[65]. Thus, the hypothalamic CRH hypersecretion may be due to the early life stress[4].

According to these hypotheses, several studies have documented a reduced hippocampal volume in adult patients with PTSD related to childhood abuse[66], as if the long-term overexposure to glucocorticoids would lead to cell atrophy, loss or decreased neurogenesis[67].

Moreover, different activation of corticolimbic pathways may induce an "overcoming" negative feedback inhibition, which causes a blunted ACTH/cortisol response after a psychosocial and not chemical stressor[4].

Another hypothesis is that the higher availability of glucocorticoid receptors on pituitary cells of PTSD patients induces an enhanced negative feedback signal on cortisol production[68,69].

An insufficient pituitary and/or adrenal response to central stimulation, or a reduced sensitivity in response to low cortisol levels, may also explain HPA axis hypersuppression[69].

Furthermore, de Kloet *et al*[69] hypothesized that subjects with PTSD display an enhanced bioavailability of Dex or an inadequate vasopressin reaction to a low dose Dex administration.

Moreover, other factors can be involved in the altered stress regulation of PTSD patients: hormone binding proteins (e.g., CRH binding protein and corticosteroid binding globulin); the immune factors; sample differences (e.g., age, gender, inclusion and exclusion criteria, presence of a comorbidity like major depressive disorder, medication use); the diurnal rhythm and pulsatile secretion of

Table 1 Hypothalamic pituitary adrenal axis functioning and its relationship with childhood traumata and psychopathology in post-traumatic stress disordered patients

Author	Control group	Sample	Cortisol levels	ACTH levels	Suppression (DST)	Stress test	Correlations with childhood traumata and psychopathology
Lemieux *et al*[46], 1995	9 non abused women; 8 abused women w/o PTSD	11 abused women with PTSD	↑ Basal urinary levels	-	-	-	↑ Scores on Impact Event Scale related to cortisol levels in PTSD sample
De Bellis *et al*[48], 1999	10 non-traumatized children; 24 healthy controls	18 children with PTSD due to childhood maltreatment	↑ Basal urinary levels	-	-	-	↑ Psychopathology
Bremner *et al*[66], 2003	18 HC	23 patients with abuse-related PTSD	Salivary cortisol: 61% higher Waiting for test; 46% higher during test	-	-	Cognitive challenge	Neurohormonal response to stress in PTSD subjects is not impaired
Luecken[52], 1998	31 HC	30 students who lost one parent before age 16	↑ Salivary levels post task	-	-	Video clip depicting the death of a parent + speech task	Altered neurohormonal responses to stress in those who lost one parent
Elzinga *et al*[53], 2003	12 abused women without PTSD	12 abused women with PTSD	Salivary cortisol: 60% higher waiting for test; 122% higher during test; 69% higher during recovery	-	-	Personalized trauma scripts	Altered neurohormonal responses to stress in PTSD abused women
Rasmusson *et al*[56], 2001	11 HC	12 outpatients with PTSD	= Plasma basal levels; ↑ plasma and urinary post tests levels	= Basal levels; ↑ post CRF levels	-	CRF and ACTH stimulation tests	Altered neurohormonal responses to stress in PTSD subjects
Santa Ana *et al*[57], 2006	31 HC	58 subjects with PTSD (25 with childhood trauma)	↓ Plasma basal and post Task, if childhood trauma	↓ Post task	-	Cold Pressor Task	-
De Bellis *et al*[58], 1994	13 HC girls	13 sexually abused girls	= Plasma and salivary basal and post CRH	↓ Basal and post CRH	-	CRH stimulation test	↑ Adult psychopathology and altered hormonal responses to stress
Stein *et al*[61], 1997	21 non abused women	19 children and/or adolescent with sexual abuse	-	-	↑	Low dose DST (0.5 mg)	↑ Adult psychopathology
Yehuda *et al*[31], 2004	10 non traumatized subjects	52 traumatized subjects	-	-	↑	Low dose DST (0.5 mg)	-
Jovanovic *et al*[59], 2010	61 traumatized non PTSD subjects	29 traumatized PTSD subjects	= Basal plasma levels; ↓ post Dex plasma levels	↓ Post Dex	↑	Low dose DST (0.5 mg)	Abnormalities of HPA feedback and ↑ psychopathology
Altemus *et al*[62], 2003	15 HC	16 women with PTSD due to childhood abuse	= Basal plasma and salivary levels	-	-	-	-
Lindley *et al*[47], 2004	17 HC	17 subjects with PTSD (88% due to childhood trauma)	↑ Basal salivary levels	-	=	Low dose DST (0.5 mg)	No correlations between cortisol, childhood abuse and psychopathology

HC: Healthy controls; DST: Dexamethasone suppression test; PTSD: Posttraumatic stress disorder; ACTH: Adrenocorticotropin hormone; CRH: Corticotropin releasing hormone; CRF: Corticotropin releasing factor.

adrenal hormones; the time passed since the traumatic event occurred; experienced stress during the assessment; the subjectivity of the perception of stressors; and alterations in the activity of the central nervous system and/or in hormone bioavailability and/or in hormone receptor function[69].

None of these hypotheses is considered completely exhaustive; thus more studies are needed in order to explain the altered functioning of the HPA axis in PTSD patients.

CHILDHOOD STRESSFUL EVENTS, HPA AXIS AND PD

Findings on HPA axis abnormalities in patients suffering from PD are conflicting and inconsistent[36], but stressful life events are known to be contributing factors[6].

Several studies have investigated the relationship between anxiety, panic attacks (PAs) and the activation of the HPA axis. In fact, anxiety and panic seem to be qualitatively different: the former is an emotional state related

Table 2 Hypothalamic pituitary adrenal axis functioning in panic disordered patients

Author	Control group	Sample	Cortisol levels	ACTH levels	DST	Stress test
Woods *et al*[71], 1987	13 HC	18 drug-free agoraphobic patients	Plasma cortisol not increased during PA	-	-	Exposure to phobic situations
Goldstein *et al*[76], 1987	61 HC; 38 outpatients with MDE	24 outpatients PD	↑ Basal plasma cortisol *vs* HC; = plasma cortisol *vs* MDE	-	=	Dex 1 mg
Cameron *et al*[74],1987	4 HC	8 PD patients	= In basal conditions; ↑ during spontaneous PA	-	-	-
Kathol *et al*[77], 1988	37 HC	65 PD subjects	↑ Urinary cortisol	-	-	-
Uhde *et al*[75], 1988	12 HC	12 drug-free PD patients	= Basal cortisol	-	-	-
Abelson *et al*[78], 1996	12 HC	20 PD subjects	↑ Overnight plasma cortisol; ↑ amplitude of ultradian secretory episodes	If low frequency of PA→ ↑ daytime ACTH levels and ↑ ACTH ultradian amplitude. If high frequency of PA→ shifted ACTH circadian cycles	-	-
Schreiber *et al*[30], 1996	10 MDE subjects, 10 HC	13 PD subjects wth agoraphobia	↑ Plasma cortisol versus controls	= Levels in PD *vs* controls and MDE subjects	92% non suppressors (higher than MDE subjects and controls)	69% abnormal Dex-CRH test (more than controls, but lesser than MDE subjects)
Bandelow *et al*[73], 2000	23 HC	23 PD patients	↑ Urinary and salivary cortisol	-	-	-
Coryell *et al*[81], 1989	38 HC	82 PD patients	-	-	25.6% non suppressors	Dex 1 mg
Coryell *et al*[80], 1991	-	72 PD patients	-	-	36% non suppressors	
Erhardt *et al*[33], 2006	30 HC	30 PD subjects	↑ Basal plasma levels	↑ Basal	-	17% hyperresponder to Dex-CRH
Petrowski *et al*[82], 2010	34 HC	34 PD subjects	= Basal salivary levels; abnormally absent cortisol awakening response	-	-	Absent cortisol response to Trier Social Stress Test
Lieberman *et al*[79], 1983	22 MDE	10 PD	↑ Plasma cortisol	-	=	DST

HC: Healthy controls; DST: Dexamethasone suppression test; PA: Panic attack; MDE: major depressive episode; ACTH: Adrenocorticotropin hormone; PD: Panic disorder; Dex: Dexamethasone; CRH: Corticotropin releasing hormone.

to a potential threat, mostly activating HPA and the sympathoadrenal axes; the latter is an emotion evoked by the perception of an actual danger that causes major sympathetic activation with small effects on the HPA axis[70].

Several authors have reported no increased salivary or plasma cortisol levels during the PA[70,71] (Table 2), maybe due to a successful habituation to the repeated experiences of panic[72]. However, probably due to anticipatory anxiety, higher salivary cortisol levels have been reported at the beginning of the PA[73,74] (Table 2).

Furthermore, several findings indicated that real life PAs and selective panicogen stimuli (e.g., sodium lactate and carbon dioxide) do not activate the HPA axis, while non-selective agents (e.g., agonists of the colecholecystokinin receptor B) induce the release of stress hormones, regardless of the occurrence of the PA[70]. On the other hand, Flumazenil and benzodiazepine receptor antagonists seem not to activate the HPA axis or induce PAs[70]. Finally, other agents, like yohimbine, mCCP and Fenfluramine, increase anticipatory anxiety and the release of stress hormones, without inducing a true PA[70].

Findings on baseline HPA axis activity and its reactivity to some stressors in panic disordered patients seem to be inconclusive (Table 2). In fact, during a resting state, both normal[74,75] and elevated cortisol levels have been reported[76-78]. On the other hand, a clear escape or hypersuppression after Dex administration has not been demonstrated[76,79], but some DST abnormalities exist and predict risk of relapse and long term disability in panic disordered subjects[30,80,81].

Furthermore, Schreiber *et al*[30] and Erhardt *et al*[33] reported a hyperresponsivity of the HPA axis to Dex/CRH test in patients with PD (Table 2), unlike Petrowski *et al*[82] who showed a lack of cortisol responsivity to acute uncontrollable stress in PD patients (Table 2).

As far as stressful life events are concerned, only Safren *et al*[5] found higher rates of childhood abuse among women with PD, than among subjects with other anxiety disorders. In fact, in most of the literature, no significant differences were found in terms of early stressful life events between PD and GAD[83], SP[84] or depression[85].

Table 3 Hypothalamic pituitary adrenal axis functioning and its correlation with psychopathology in obsessive compulsive disordered patients

Author	Control group	Sample	Cortisol levels	Other hormones levels	DST	Correlations with psychopathology
Monteleone *et al*[91], 1994	13 HC	13 drug-free OCD patients	↑ Plasma cortisol cyrcadian rhythm	-	-	↑ Severity of OCD symptoms
Kluge *et al*[86], 2007	9 HC	9 OCD inpatients w/o comorbid depression	↑ Plasma levels	↑ Plasma ACTH	-	-
Catapano *et al*[89], 1990	20 HC	18 OCD patients	-	-	27.7% non-suppression	Correlated with sex (all non suppressors were males) and independently of depression
Coryell *et al*[92], 1989	82 panic disordered patients	20 OCD outpatients	-	-	=	-
Altemus *et al*[90], 1992	25 HC	12 OCD subjects	-	↑ CSF CRH; ↑ plasma and CSF AVP	-	↑ Psychopathology

HC: Healthy controls; DST: Dexamethasone suppression test; CSF: Cerebrospinal fluid; CRH: Corticotropin releasing hormone; AVP: Arginine vasopressin; OCD: Obsessive-compulsive disorder; ACTH: Adrenocorticotropin hormone.

In conclusion, stressful life events may have a triggering function but they are not a *conditio sine qua non* that supports the development of PD[6] and data concerning HPA axis functioning are discordant, as both normal and increased hormonal activity have been reported[70,73].

CHILDHOOD STRESSFUL EVENTS, HPA AXIS AND OCD

A large number of studies reported that the onset of OCD is often preceded by stressful events, like increased responsibility (e.g., job promotion, birth of a child), losses (e.g., death of a family member, dismissal from employment) and traumata, such as abuse or combat[86]. Moreover, it is well documented that OCD symptoms increase under stressful situations[87] and that patients with OCD suffer from daily life stress more than healthy controls[87,88].

However, data about the relationship between stress, HPA axis functioning and OCD are scarce and discordant[86], even if several studies have shown an increased activity of the HPA axis in OCD disordered patients[86,89-91] (Table 3).

For instance, Kluge *et al*[86] demonstrated that nocturnal plasma cortisol and ACTH levels were significantly elevated in patients with OCD, compared to healthy controls. The circadian rhythm of cortisol was preserved in OCD patients, although at a higher level compared with normal controls and proportional to the severity of obsessive-compulsive symptoms[91]. Furthermore, CRH and AVP levels have been found significantly elevated in the CSF and plasma of these patients, compared to healthy controls[90] (Table 3). Catapano *et al*[89] observed that a subgroup of OCD patients, particularly males, may escape the DST independently from the coexistence of depressive features. On the other hand, Coryell *et al*[92] reported normal suppression after 1 mg Dex (Table 3).

Moreover, the role of the stress responsive neurohormone AVP in the onset and maintenance of compulsive behaviors (e.g., hand-washing, cleaning and trichotillomania) has been studied in rats. The intracerebroventricular administration of ACTH or CRH in rats prolongs the maintenance of conditioned behaviors acquired during a period of stress (i.e., induction of aversive stimuli, like shocks and loud noises), and promotes grooming, which is considered a behavioral model for OCD[86,93]. In humans, the intranasal administration of vasopressin seems to narrow the focus of attention and influence cognitive processes, similar to the focused-obsessive thoughts and compulsive rituals of obsessive-compulsive patients[90].

Finally, structural neuroimaging studies observed dysfunctioning in OCD patients' anterior cingulated gyrus, which is known to be involved in the regulation of the HPA axis[94,95].

In conclusion, obsessive-compulsive disordered subjects show a hyperactivity of the HPA axis but the increased hormonal levels might be a consequence of stress[7] or, vice versa, they might be involved in the pathophysiology of OCD, sustaining clinical features like perseverative or grooming behaviors[86].

CHILDHOOD STRESSFUL EVENTS, HPA AXIS AND SP

Several authors hypothesized that early stressful life events (including separation from parents, parents' marital discord, sexual/physical/emotional abuse, familial violence, childhood diseases) and parental rearing styles (such as neglect and family history of psychiatric disorders, like anxiety disorders, depression and suicidality) have a role in the onset of SP and may increase the severity of social phobic symptoms[5,55,96-98].

Accordingly, sexual and/or physical abuse were most specifically associated with SP and childhood abuse seems to be an important risk factor for the development of this disorder[4,97,98].

Table 4 Hypothalamic pituitary adrenal axis functioning and its correlation with psychopathology and childhood traumata in social phobia patients

Author	Control group	Sample	Cortisol levels	CRH levels	Stress test	Correlations with childhood traumata and psychopathology
Potts *et al*[100], 1991	15 HC	10 SP	= Urinary	-	-	-
Levin *et al*[103], 1993	14 HC	36 (28 generalized SP + 8 specific SP)	= Plasma	-	Ten-minute talk	-
Uhde *et al*[101], 1994	-	54-64 SP patients	= Plasma and urinary	-	= DST (Dex 1 mg)	-
Martel *et al*[105], 1999	21 HC	27 SP	= Salivary basal and task-related	-	Modified TSST	Correlated to anticipatory anxiety in both groups
Furlan *et al*[104], 2001	17 HC	18 SP	After speech task: ↑ 90% increase in salivary levels in 7 SP; ↓ 32% in salivary LE in 11 SP. After exercise task: =	-	Public speaking task and physical exercise task	-
Condren *et al*[32], 2002	15 HC	15 SP	↑ Plasma cortisol after test; = plasma cortisol basal	= Basal and after test	Public mental arithmetic and short term memory test	-
van West *et al*[106], 2008	25 HC	25 SP	↑ Salivary cortisol after test	-	Public speaking test	Correlated to trait but not state anxiety levels
Roelofs *et al*[107], 2009	22 HC, 17 patients with PTSD	18 SP	↑ Salivary cortisol after test	-	Social approach-avoidance task in social stress condition (TSST)	Cortisol increase correlated to the social avoidance behavior
Elzinga *et al*[99], 2010	16 SAD w/o CA, 16 HC, 16 PTSD with CA	9 SAD with CA	↑ Salivary cortisol after test; = salivary cortisol basal	-	TSST	CA is associated with ↑ cortisol reactivity to TSST
Lanzenberger *et al*[102], 2010	18 HC	12 subjects with SP	↓ Plasma levels	-	-	Negative correlations with 5HT binding in brain regions and positive correlation with trait anxiety

HC: Healthy controls; DST: Dexamethasone suppression test; TSST: Trier social stress test; SAD: Separation anxiety disorder; CA: Childhood abuse; SP: Social phobia; PTSD: Posttraumatic stress disorder; Dex: Dexamethasone.

Moreover, in line with the hypothesis that SP is a stress-related condition, HPA axis hyperactivity can represent the linkage between stressful events and the onset and development of this disorder[4,11].

Elzinga *et al*[99] found a significant association between a history of childhood abuse (emotional, physical or sexual abuse) and enhanced cortisol reactivity to a psychosocial stress task in patients with SP, although any difference in baseline cortisol levels has been reported between SP patients, PTSD patients and healthy controls (Table 4).

Moreover, several authors reported normal basal HPA axis functioning in adult social phobics[100,101] (Table 4). Mean basal morning plasma cortisol levels were significantly lower in patients with SP, than in healthy control subjects, and a significant correlation between cortisol plasma levels and trait but non state anxiety scores seems to exist[102] (Table 4).

Conflicting results are reported after a stress test (Table 4). Levin *et al*[103] found decreased plasma cortisol levels in response to a public speaking task, both in adult patients with SP and normal controls. Furlan *et al*[104] found that SP patients display a bimodal salivary cortisol response and a larger increase in salivary cortisol levels following a speech task, but any difference from normal subjects has been reported, under physical stress or basal conditions (Table 4).

Martel *et al*[105] observed similar salivary cortisol levels in social phobic adolescent girls and controls, in response to a modified trier social stress test (TSST), even if cortisol levels appeared to be a sensitive measure of anticipatory anxiety prior to the performance task in both groups (Table 4). On the other hand, van West *et al*[106] reported that prepubertal subjects with social anxiety show elevated salivary cortisol response to a psychosocial stressor (Table 4).

The hyper-responsiveness of the adrenal cortex during the psychosocial stressor and the similar basal levels of cortisol with respect to controls were also confirmed by Condren *et al*[32] (Table 4).

Recently, Roelofs *et al*[107] provided the first evidence for a direct link between increased cortisol stress-responsiveness and social avoidance behavior in SP patients (Table 4). During a social approach avoidance task in a social stress condition (provided by the TSST), social phobics showed increased cortisol responses compared to healthy participants and PTSD patients. Moreover, social stress elicited increased avoidance tendencies towards

Table 5 Hypothalamic pituitary adrenal axis functioning and its correlations with psychopathology in generalized anxiety disordered patients

Author	Control group	Sample	Cortisol levels	DST	Correlations with psychopathology
Mantella *et al*[114], 2008	42 HC	71 GAD subjects	↑ Morning basal and peak salivary cortisol	-	↑ Psychopathology
Steudte *et al*[118], 2011	15 HC	15 GAD patients	↓ Cortisol in the first and second 3-cm hair segments; = salivary diurnal cortisol profiles	-	-
Schweizer *et al*[112], 1986	-	79 GAD subjects	-	27% non-suppression	-
Tiller *et al*[113], 1988	13 HC	30 GAD patients	-	27% non-suppression	Normalization of HPAA suppression after successful non drug behavioral treatment
Tafet *et al*[115], 2005	8 non treated GAD outpatients	17 treated GAD outpatients	= Morning plasma cortisol; ↑ evening plasma cortisol	-	↓ Evening plasma cortisol level after cognitive treatment
Pomara *et al*[116], 2005	90 HC	41 GAD patients	↑ Plasma cortisol levels	-	↓ Plasma cortisol after acute and chronic treatment with diazepam
Rosenbaum *et al*[117], 1983	22 HC	22 GAD subjects	= 24 h urinary cortisol levels	-	-

HC: Healthy controls; DST: Dexamethasone suppression test; GAD: Generalized anxiety disorder; HPAA: Hypothalamic pituitary adrenal axis.

social threat stimuli in SP patients and this behavior was predicted by cortisol responses[107].

Moreover, stating that shyness, separation anxiety disorder (SAD) and behavioral inhibition (BI) have been postulated to be precursors of SP[108], high cortisol levels have been reported in shy children and adults[29,109], in children suffering from SAD[110], and in children with BI[111]. Some authors have hypothesized that the increased CRH and cortisol levels of these children can exacerbate their fearfulness and predispose them to develop SP[109].

In conclusion, a hyper-responsiveness of the adrenal cortex has been reported in social phobics, mainly during a psychosocial stressor[32,104,106,107], while findings at baseline are similar to those of controls[32,107]. However, several authors have hypothesized that HPA axis hyperactivity may link early stressful events to the development of SP[11,40,99].

CHILDHOOD STRESSFUL EVENTS, HPA AXIS AND GAD

Few studies have examined HPA axis activity in GAD, even if the persistent excessive anxiety and uncontrollable worry about a variety of events and situations that characterize GAD patients[2] suggest that these subjects are exposed to repeated stressful experiences, which could consequently lead to an altered cortisol secretory pattern.

The first investigations on HPA axis functioning in GAD used the DST (Table 5). Non-suppression rates of 27% were reported[112,113], suggesting a reduced negative feedback sensitivity of the HPA axis.

More recently, Mantella *et al*[114] showed that elderly individuals with GAD exhibited a 40%-50% increase in basal salivary cortisol levels, with higher peak cortisol levels and larger areas under the curve, compared to matched control subjects (Table 5). Additionally, severity of GAD, as measured by psychometric instruments, was positively correlated with cortisol levels[114]. Also Tafet *et al*[115] and Pomara *et al*[116] observed that patients with GAD presented increased levels of circulating cortisol (Table 5). Tafet *et al*[115] reported that cognitive therapy (CT) was effective in improving distressful clinical symptoms of GAD and in recovering psychoneuroendocrinological functions of these subjects. In fact, after a maximum of 24 sessions of CT, a significant decrease in the Hamilton Anxiety Rating Scale and a significant decrease in previously increased levels of circulating cortisol were observed[115]. Pharmacological therapy also showed its efficacy in the treatment of GAD: reductions of anxiety symptoms and plasma cortisol levels were reported after acute and chronic diazepam treatment, even if independent of GAD status and drug dosage[116].

On the other hand, other studies failed to show aberrant adrenocortical activity in GAD: similar 24 h urinary cortisol levels[117] and plasma cortisol levels[118] were observed in GAD patients and healthy controls (Table 5).

Finally, Steudte *et al*[118] studied cortisol secretion using hair analysis, which provides a retrospective reflection of cortisol secretion for a period up to 6 mo. Results showed significantly lower (50%-60%) cortisol levels in the first and second 3 cm hair segments of GAD patients, compared to those of controls, while no group difference in salivary diurnal cortisol profiles was observed (Table 5). An attempt to explain this finding is that, under naturalistic conditions, GAD may be associated with hypocortisolism, similar to healthy individuals living under chronic stress conditions and to patients with several bodily disorders (like chronic fatigue syndrome, fibromyalgia, other somatoform disorders, rheumatoid arthritis and asthma)[119,120].

In conclusion, different studies suggest that GAD

is associated with hypercortisolism. A possible explanation of this finding is that chronic stress, along with the inadequacy to cope with it or the perceived loss of controllability, may lead to persistent HPA axis activation and the sustained increase of cortisol levels[121]. Moreover, the unremitting activation of the HPA axis is supposed to be mediated by changes in the sensitivity, or in the number, of CRH and/or glucocorticoid receptors of the hippocampus, limbic system and cortical levels (brain areas associated with anxiety disorders). Thus, it is possible that the autoregulatory feedback of GAD is not as efficient as in healthy subjects and cortisol hypersecretion is not downregulated[114].

Furthermore, GAD patients report a high rate of childhood physical or sexual abuse that can be associated with an alteration of the HPA axis and can contribute to the onset and maintenance of the disorder[5].

DISCUSSION

Data concerning the relationship between childhood stressful life events, HPA axis and anxiety disorders have been reviewed.

The vast majority of studies agreed on the hyperactivity of the HPA axis[40] and high rates of early stressful life events[3-5,12] in anxiety disorders. However, conflicting results on HPA axis functioning emerged from this review: patients with PTSD show baseline high CRH levels and low plasma cortisol levels; both normal and increased hormonal activity have been reported in PD patients[70,73]; OCD subjects show a hyperactivity of HPA axis[86,89-91]; a hyper-responsiveness of the adrenal cortex has been reported in social phobics after a psychosocial stressor[32,104,106,107], but normal levels have been observed at baseline[32,101]; and lastly, several studies suggest that GAD is associated with hypercortisolism[112-116].

Several hypotheses have been proposed in order to explain these discordant data. The first is the effect of comorbidity that might explain some of the differences in HPA axis activity among comorbid depressed patients[122].

Another explanation is based on the cognitive/emotional modulation, as some authors observed a normalization of the HPA axis of panic patients after treatment[36].

A third hypothesis develops from the habituation phenomena. In fact, individuals with high and persistent anxiety levels feel stressed regularly, showing a state of chronic adrenal stress hyper-reactivity and persistently elevated cortisol concentrations. These effects may influence HPA axis functioning, inducing a sort of counter-regulative adaptation and thus downregulating HPA axis stress responsivity[8,16]. Hence, high and persistent levels of anxiety could be associated with low cortisol concentrations[123,124], reflecting resilience rather than a risk for psychopathology[8,16].

On the other hand, elevations in cortisol levels that persist across time could also tune HPA axis activity to a higher level and could result in damage of the hippocampal glucocorticoid receptors or even a loss of hippocampal neurons[66], reducing the negative feedback of CRH secretion and resulting in higher CRH and cortisol concentrations[124].

Furthermore, the link between childhood adverse experiences, HPA axis abnormalities and anxiety disorders has not been studied carefully. A well accepted hypothesis is that stressful life events, not being specific of any psychiatric disorder, can act as triggers on HPA axis dysregulation, predicting a general vulnerability to anxiety and mood disorders[4,5,11].

In line with these observations, some authors have hypothesized that the neuroendocrine alterations after an early stress can result in a biological 'wound' that increases the individual's vulnerability to stressors later in life and, thus, predisposes an individual to develop mood or anxiety disorders that are known to manifest or worsen in relationship to acute or chronic life stress[3-5,7,11,96]. In fact, once the HPA axis is over-activated during the developmental processes, it remains permanently unstable, overdriven, vulnerable or dysfunctional[7,16,125], possibly due to transcriptional/epigenomic mechanisms[126,127].

However, a retrospective recall bias may influence the assessment of early events in several ways[11]. The poor reliability of the memories relevant to childhood[9,10], the "search for meaning", by which the subjects tend to search for reasons for the present distress in their past experiences, and the attitude of the interviewer, who may or may not encourage the patient, all affect the accurate retrieval of past events[11].

In conclusion, the review of the available literature supports an alteration of the HPA axis in anxiety disordered patients but the relationship with early stressful life events is still to be elucidated. Authors conclude that childhood life events and HPA abnormalities may be aspecifically and transnosographically related, not only to all anxiety disorders, but broadly to all psychiatric disorders. Thus, studying the role of early stressful life events in the later development of anxiety disorders may help clinicians in the prevention and treatment of these disorders.

REFERENCES

1 **Kessler RC**, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 617-627

2 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (DMS-IV-TR). Washington, DC: American Psychiatric Association, 2000

3 **Arborelius L**, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotropin-releasing factor in depression and anxiety disorders. *J Endocrinol* 1999; **160**: 1-12

4 **Heim C**, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol Psychiatry* 2001; **49**: 1023-1039

5 **Safren SA**, Gershuny BS, Marzol P, Otto MW, Pollack MH. History of childhood abuse in panic disorder, social phobia, and generalized anxiety disorder. *J Nerv Ment Dis* 2002; **190**:

453-456
6 **Bandelow B**, Späth C, Tichauer GA, Broocks A, Hajak G, Rüther E. Early traumatic life events, parental attitudes, family history, and birth risk factors in patients with panic disorder. *Compr Psychiatry* 2002; **43**: 269-278
7 **Nemeroff CB CB**. Early-Life Adversity, CRF Dysregulation, and Vulnerability to Mood and Anxiety Disorders. *Psychopharmacol Bull* 2004; **38**: 14-20
8 **Carpenter LL**, Carvalho JP, Tyrka AR, Wier LM, Mello AF, Mello MF, Anderson GM, Wilkinson CW, Price LH. Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biol Psychiatry* 2007; **62**: 1080-1087
9 **Copeland WE**, Keeler G, Angold A, Costello EJ. Traumatic events and posttraumatic stress in childhood. *Arch Gen Psychiatry* 2007; **64**: 577-584
10 **Zlotnick C**, Johnson J, Kohn R, Vicente B, Rioseco P, Saldivia S. Childhood trauma, trauma in adulthood, and psychiatric diagnoses: results from a community sample. *Compr Psychiatry* 2008; **49**: 163-169
11 **Faravelli C**, Gorini Amedei S, Rotella F, Faravelli L, Palla A, Consoli G, Ricca V, Batini S, Lo Sauro C, Spiti A, Catena Dell' osso M. Childhood traumata, Dexamethasone Suppression Test and psychiatric symptoms: a trans-diagnostic approach. *Psychol Med* 2010; **40**: 2037-2048
12 **Schoedl AF**, Costa MC, Mari JJ, Mello MF, Tyrka AR, Carpenter LL, Price LH. The clinical correlates of reported childhood sexual abuse: an association between age at trauma onset and severity of depression and PTSD in adults. *J Child Sex Abus* 2010; **19**: 156-170
13 **Bennett AJ**, Lesch KP, Heils A, Long JC, Lorenz JG, Shoaf SE, Champoux M, Suomi SJ, Linnoila MV, Higley JD. Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Mol Psychiatry* 2002; **7**: 118-122
14 **Breier A**, Kelsoe JR, Kirwin PD, Beller SA, Wolkowitz OM, Pickar D. Early parental loss and development of adult psychopathology. *Arch Gen Psychiatry* 1988; **45**: 987-993
15 **Charmandari E**, Kino T, Souvatzoglou E, Chrousos GP. Pediatric stress: hormonal mediators and human development. *Horm Res* 2003; **59**: 161-179
16 **Tyrka AR**, Wier L, Price LH, Ross N, Anderson GM, Wilkinson CW, Carpenter LL. Childhood parental loss and adult hypothalamic-pituitary-adrenal function. *Biol Psychiatry* 2008; **63**: 1147-1154
17 **de Kloet ER**, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci* 2005; **6**: 463-475
18 **Sapolsky RM**, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev* 2000; **21**: 55-89
19 **de Kloet ER**. Hormones, brain and stress. *Endocr Regul* 2003; **37**: 51-68
20 **Brenes Sáenz JC**, Villagra OR, Fornaguera Trías J. Factor analysis of Forced Swimming test, Sucrose Preference test and Open Field test on enriched, social and isolated reared rats. *Behav Brain Res* 2006; **169**: 57-65
21 **Levine S**, Johnson DF, Gonzalez CA. Behavioral and hormonal responses to separation in infant rhesus monkeys and mothers. *Behav Neurosci* 1985; **99**: 399-410
22 **Hennessy MB**, Moorman L. Factors influencing cortisol and behavioral responses to maternal separation in guinea pigs. *Behav Neurosci* 1989; **103**: 378-385
23 **Dunn AJ**, Berridge CW. Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress responses? *Brain Res Brain Res Rev* 1990; **15**: 71-100
24 **Owens MJ**, Nemeroff CB. Physiology and pharmacology of corticotropin-releasing factor. *Pharmacol Rev* 1991; **43**: 425-473
25 **Weiss JM**, Stout JC, Aaron MF, Quan N, Owens MJ, Butler PD, Nemeroff CB. Depression and anxiety: role of the locus coeruleus and corticotropin-releasing factor. *Brain Res Bull* 1994; **35**: 561-572
26 **Flinn MV**, Quinlan RJ, Decker SA, Turner MT, England BG. Male-female differences in effects of parental absence on glucocorticoid stress response. *Human Nature* 1996; **7**: 125-162
27 **Pfeffer CR**, Altemus M, Heo M, Jiang H. Salivary cortisol and psychopathology in children bereaved by the september 11, 2001 terror attacks. *Biol Psychiatry* 2007; **61**: 957-965
28 **Weller EB**, Weller RA, Fristad MA, Bowes JM. Dexamethasone suppression test and depressive symptoms in bereaved children: a preliminary report. *J Neuropsychiatry Clin Neurosci* 1990; **2**: 418-421
29 **Tyrka AR**, Wier LM, Price LH, Rikhye K, Ross NS, Anderson GM, Wilkinson CW, Carpenter LL. Cortisol and ACTH responses to the Dex/CRH test: influence of temperament. *Horm Behav* 2008; **53**: 518-525
30 **Schreiber W**, Lauer CJ, Krumrey K, Holsboer F, Krieg JC. Dysregulation of the hypothalamic-pituitary-adrenocortical system in panic disorder. *Neuropsychopharmacology* 1996; **15**: 7-15
31 **Yehuda R**, Halligan SL, Golier JA, Grossman R, Bierer LM. Effects of trauma exposure on the cortisol response to dexamethasone administration in PTSD and major depressive disorder. *Psychoneuroendocrinology* 2004; **29**: 389-404
32 **Condren RM**, O'Neill A, Ryan MC, Barrett P, Thakore JH. HPA axis response to a psychological stressor in generalised social phobia. *Psychoneuroendocrinology* 2002; **27**: 693-703
33 **Erhardt A**, Ising M, Unschuld PG, Kern N, Lucae S, Pütz B, Uhr M, Binder EB, Holsboer F, Keck ME. Regulation of the hypothalamic-pituitary-adrenocortical system in patients with panic disorder. *Neuropsychopharmacology* 2006; **31**: 2515-2522
34 **Delahanty DL**, Nugent NR. Predicting PTSD prospectively based on prior trauma history and immediate biological responses. *Ann N Y Acad Sci* 2006; **1071**: 27-40
35 **Griffin MG**, Resick PA, Yehuda R. Enhanced cortisol suppression following dexamethasone administration in domestic violence survivors. *Am J Psychiatry* 2005; **162**: 1192-1199
36 **Abelson JL**, Khan S, Liberzon I, Young EA. HPA axis activity in patients with panic disorder: review and synthesis of four studies. *Depress Anxiety* 2007; **24**: 66-76
37 **Kallen VL**, Tulen JH, Utens EM, Treffers PD, De Jong FH, Ferdinand RF. Associations between HPA axis functioning and level of anxiety in children and adolescents with an anxiety disorder. *Depress Anxiety* 2008; **25**: 131-141
38 **MacKenzie EM**, Odontiadis J, Le Mellédo JM, Prior TI, Baker GB. The relevance of neuroactive steroids in schizophrenia, depression, and anxiety disorders. *Cell Mol Neurobiol* 2007; **27**: 541-574
39 **Risbrough VB**, Stein MB. Role of corticotropin releasing factor in anxiety disorders: a translational research perspective. *Horm Behav* 2006; **50**: 550-561
40 **Vreeburg SA**, Zitman FG, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, Hoogendijk WJ, Smit JH, Penninx BW. Salivary cortisol levels in persons with and without different anxiety disorders. *Psychosom Med* 2010; **72**: 340-347
41 **Bremner D**, Vermetten E, Kelley ME. Cortisol, dehydroepiandrosterone, and estradiol measured over 24 hours in women with childhood sexual abuse-related posttraumatic stress disorder. *J Nerv Ment Dis* 2007; **195**: 919-927
42 **Heim C**, Mletzko T, Purselle D, Musselman DL, Nemeroff CB. The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biol Psychiatry* 2008; **63**: 398-405
43 **Lang AJ**, Aarons GA, Gearity J, Laffaye C, Satz L, Dresselhaus TR, Stein MB. Direct and indirect links between childhood maltreatment, posttraumatic stress disorder, and women's health. *Behav Med* 2008; **33**: 125-135
44 **Yanos PT**, Czaja SJ, Widom CS. A prospective examination

of service use by abused and neglected children followed up into adulthood. *Psychiatr Serv* 2010; **61**: 796-802
45 **Yehuda R**, Flory JD, Pratchett LC, Buxbaum J, Ising M, Holsboer F. Putative biological mechanisms for the association between early life adversity and the subsequent development of PTSD. *Psychopharmacology* (Berl) 2010; **212**: 405-417
46 **Lemieux AM**, Coe CL. Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. *Psychosom Med* 1995; **57**: 105-115
47 **Lindley SE**, Carlson EB, Benoit M. Basal and dexamethasone suppressed salivary cortisol concentrations in a community sample of patients with posttraumatic stress disorder. *Biol Psychiatry* 2004; **55**: 940-945
48 **De Bellis MD**, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, Jenkins FJ, Ryan ND. A.E. Bennett Research Award. Developmental traumatology. Part I: Biological stress systems. *Biol Psychiatry* 1999; **45**: 1259-1270
49 **Bremner JD**, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM, Nemeroff CB, Charney DS. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *Am J Psychiatry* 1997; **154**: 624-629
50 **Baker DG**, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geracioti TD. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. *Am J Psychiatry* 1999; **156**: 585-588
51 **Pervanidou P**, Chrousos GP. Neuroendocrinology of posttraumatic stress disorder. *Prog Brain Res* 2010; **182**: 149-160
52 **Luecken LJ**. Childhood attachment and loss experiences affect adult cardiovascular and cortisol function. *Psychosom Med* 1998; **60**: 765-772
53 **Elzinga BM**, Schmahl CG, Vermetten E, van Dyck R, Bremner JD. Higher cortisol levels following exposure to traumatic reminders in abuse-related PTSD. *Neuropsychopharmacology* 2003; **28**: 1656-1665
54 **Bremner JD**, Vythilingam M, Vermetten E, Adil J, Khan S, Nazeer A, Afzal N, McGlashan T, Elzinga B, Anderson GM, Heninger G, Southwick SM, Charney DS. Cortisol response to a cognitive stress challenge in posttraumatic stress disorder (PTSD) related to childhood abuse. *Psychoneuroendocrinology* 2003; **28**: 733-750
55 **Heim C**, Newport DJ, Bonsall R, Miller AH, Nemeroff CB. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *Am J Psychiatry* 2001; **158**: 575-581
56 **Rasmusson AM**, Lipschitz DS, Wang S, Hu S, Vojvoda D, Bremner JD, Southwick SM, Charney DS. Increased pituitary and adrenal reactivity in premenopausal women with posttraumatic stress disorder. *Biol Psychiatry* 2001; **50**: 965-977
57 **Santa Ana EJ**, Saladin ME, Back SE, Waldrop AE, Spratt EG, McRae AL, LaRowe SD, Timmerman MA, Upadhyaya H, Brady KT. PTSD and the HPA axis: differences in response to the cold pressor task among individuals with child vs. adult trauma. *Psychoneuroendocrinology* 2006; **31**: 501-509
58 **De Bellis MD**, Chrousos GP, Dorn LD, Burke L, Helmers K, Kling MA, Trickett PK, Putnam FW. Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *J Clin Endocrinol Metab* 1994; **78**: 249-255
59 **Jovanovic T**, Norrholm SD, Blanding NQ, Phifer JE, Weiss T, Davis M, Duncan E, Bradley B, Ressler K. Fear potentiation is associated with hypothalamic-pituitary-adrenal axis function in PTSD. *Psychoneuroendocrinology* 2010; **35**: 846-857
60 **Newport DJ**, Heim C, Bonsall R, Miller AH, Nemeroff CB. Pituitary-adrenal responses to standard and low-dose dexamethasone suppression tests in adult survivors of child abuse. *Biol Psychiatry* 2004; **55**: 10-20
61 **Stein MB**, Yehuda R, Koverola C, Hanna C. Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. *Biol Psychiatry* 1997; **42**: 680-686
62 **Altemus M**, Cloitre M, Dhabhar FS. Enhanced cellular immune response in women with PTSD related to childhood abuse. *Am J Psychiatry* 2003; **160**: 1705-1707
63 **Nemeroff CB**. The preeminent role of early untoward experience on vulnerability to major psychiatric disorders: the nature-nurture controversy revisited and soon to be resolved. *Mol Psychiatry* 1999; **4**: 106-108
64 **Yehuda R**, Resnick H, Kahana B, Giller EL. Long-lasting hormonal alterations to extreme stress in humans: normative or maladaptive? *Psychosom Med* 1993; **55**: 287-297
65 **Yehuda R**, Southwick SM, Nussbaum G, Wahby V, Giller EL, Mason JW. Low urinary cortisol excretion in patients with posttraumatic stress disorder. *J Nerv Ment Dis* 1990; **178**: 366-369
66 **Bremner JD**, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, Khan S, Vaccarino LV, Soufer R, Garg PK, Ng CK, Staib LH, Duncan JS, Charney DS. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry* 2003; **160**: 924-932
67 **Duman RS**, Charney DS. Cell atrophy and loss in major depression. *Biol Psychiatry* 1999; **45**: 1083-1084
68 **Yehuda R**, Boisoneau D, Lowy MT, Giller EL. Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. *Arch Gen Psychiatry* 1995; **52**: 583-593
69 **de Kloet CS**, Vermetten E, Geuze E, Kavelaars A, Heijnen CJ, Westenberg HG. Assessment of HPA-axis function in posttraumatic stress disorder: pharmacological and non-pharmacological challenge tests, a review. *J Psychiatr Res* 2006; **40**: 550-567
70 **Graeff FG**, Garcia-Leal C, Del-Ben CM, Guimarães FS. Does the panic attack activate the hypothalamic-pituitary-adrenal axis? *An Acad Bras Cienc* 2005; **77**: 477-491
71 **Woods SW**, Charney DS, McPherson CA, Gradman AH, Heninger GR. Situational panic attacks. Behavioral, physiologic, and biochemical characterization. *Arch Gen Psychiatry* 1987; **44**: 365-375
72 **Schommer NC**, Hellhammer DH, Kirschbaum C. Dissociation between reactivity of the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenal-medullary system to repeated psychosocial stress. *Psychosom Med* 2003; **65**: 450-460
73 **Bandelow B**, Wedekind D, Sandvoss V, Broocks A, Hajak G, Pauls J, Peter H, Rüther E. Diurnal variation of cortisol in panic disorder. *Psychiatry Res* 2000; **95**: 245-250
74 **Cameron OG**, Lee MA, Curtis GC, McCann DS. Endocrine and physiological changes during «spontaneous» panic attacks. *Psychoneuroendocrinology* 1987; **12**: 321-331
75 **Uhde TW**, Joffe RT, Jimerson DC, Post RM. Normal urinary free cortisol and plasma MHPG in panic disorder: clinical and theoretical implications. *Biol Psychiatry* 1988; **23**: 575-585
76 **Goldstein S**, Halbreich U, Asnis G, Endicott J, Alvir J. The hypothalamic-pituitary-adrenal system in panic disorder. *Am J Psychiatry* 1987; **144**: 1320-1323
77 **Kathol RG**, Noyes R, Lopez AL, Reich JH. Relationship of urinary free cortisol levels in patients with panic disorder to symptoms of depression and agoraphobia. *Psychiatry Res* 1988; **24**: 211-221
78 **Abelson JL**, Curtis GC. Hypothalamic-pituitary-adrenal axis activity in panic disorder. 24-hour secretion of corticotropin and cortisol. *Arch Gen Psychiatry* 1996; **53**: 323-331
79 **Lieberman JA**, Brenner R, Lesser M, Coccaro E, Borenstein M, Kane JM. Dexamethasone suppression tests in patients with panic disorder. *Am J Psychiatry* 1983; **140**: 917-919
80 **Coryell W**, Noyes R, Reich J. The prognostic significance of HPA-axis disturbance in panic disorder: a three-year follow-up. *Biol Psychiatry* 1991; **29**: 96-102
81 **Coryell W**, Noyes R, Schlechte J. The significance of HPA

axis disturbance in panic disorder. *Biol Psychiatry* 1989; **25**: 989-1002
82 **Petrowski K**, Herold U, Joraschky P, Wittchen HU, Kirschbaum C. A striking pattern of cortisol non-responsiveness to psychosocial stress in patients with panic disorder with concurrent normal cortisol awakening responses. *Psychoneuroendocrinology* 2010; **35**: 414-421
83 **Raskin M**, Peeke HV, Dickman W, Pinsker H. Panic and generalized anxiety disorders. Developmental antecedents and precipitants. *Arch Gen Psychiatry* 1982; **39**: 687-689
84 **Zitrin CM**, Ross DC. Early separation anxiety and adult agoraphobia. *J Nerv Ment Dis* 1988; **176**: 621-625
85 **Coryell W**, Noyes R, Clancy J. Panic disorder and primary unipolar depression. A comparison of background and outcome. *J Affect Disord* 1983; **5**: 311-317
86 **Kluge M**, Schüssler P, Künzel HE, Dresler M, Yassouridis A, Steiger A. Increased nocturnal secretion of ACTH and cortisol in obsessive compulsive disorder. *J Psychiatr Res* 2007; **41**: 928-933
87 **Coles ME**, Heimberg RG, Frost RO, Steketee G. Not just right experiences and obsessive-compulsive features: experimental and self-monitoring perspectives. *Behav Res Ther* 2005; **43**: 153-167
88 **Findley DB**, Leckman JF, Katsovich L, Lin H, Zhang H, Grantz H, Otka J, Lombroso PJ, King RA. Development of the Yale Children's Global Stress Index (YCGSI) and its application in children and adolescents ith Tourette's syndrome and obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 2003; **42**: 450-457
89 **Catapano F**, Monteleone P, Maj M, Kemali D. Dexamethasone suppression test in patients with primary obsessive-compulsive disorder and in healthy controls. *Neuropsychobiology* 1990; **23**: 53-56
90 **Altemus M**, Pigott T, Kalogeras KT, Demitrack M, Dubbert B, Murphy DL, Gold PW. Abnormalities in the regulation of vasopressin and corticotropin releasing factor secretion in obsessive-compulsive disorder. *Arch Gen Psychiatry* 1992; **49**: 9-20
91 **Monteleone P**, Catapano F, Del Buono G, Maj M. Circadian rhythms of melatonin, cortisol and prolactin in patients with obsessive-compulsive disorder. *Acta Psychiatr Scand* 1994; **89**: 411-415
92 **Coryell WH**, Black DW, Kelly MW, Noyes R. HPA axis disturbance in obsessive-compulsive disorder. *Psychiatry Res* 1989; **30**: 243-251
93 **Joel D**. Current animal models of obsessive compulsive disorder: a critical review. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; **30**: 374-388
94 **Rosenberg DR**, Keshavan MS. A.E. Bennett Research Award. Toward a neurodevelopmental model of of obsessive--compulsive disorder. *Biol Psychiatry* 1998; **43**: 623-640
95 **Ursu S**, Stenger VA, Shear MK, Jones MR, Carter CS. Overactive action monitoring in obsessive-compulsive disorder: evidence from functional magnetic resonance imaging. *Psychol Sci* 2003; **14**: 347-353
96 **Bandelow B**, Charimo Torrente A, Wedekind D, Broocks A, Hajak G, Rüther E. Early traumatic life events, parental rearing styles, family history of mental disorders, and birth risk factors in patients with social anxiety disorder. *Eur Arch Psychiatry Clin Neurosci* 2004; **254**: 397-405
97 **Gibb BE**, Chelminski I, Zimmerman M. Childhood emotional, physical, and sexual abuse, and diagnoses of depressive and anxiety disorders in adult psychiatric outpatients. *Depress Anxiety* 2007; **24**: 256-263
98 **Simon NM**, Herlands NN, Marks EH, Mancini C, Letamendi A, Li Z, Pollack MH, Van Ameringen M, Stein MB. Childhood maltreatment linked to greater symptom severity and poorer quality of life and function in social anxiety disorder. *Depress Anxiety* 2009; **26**: 1027-1032
99 **Elzinga BM**, Spinhoven P, Berretty E, de Jong P, Roelofs K. The role of childhood abuse in HPA-axis reactivity in Social Anxiety Disorder: a pilot study. *Biol Psychol* 2010; **83**: 1-6
100 **Potts NL**, Davidson JR, Krishnan KR, Doraiswamy PM, Ritchie JC. Levels of urinary free cortisol in social phobia. *J Clin Psychiatry* 1991; **52** Suppl: 41-42
101 **Uhde TW**, Tancer ME, Gelernter CS, Vittone BJ. Normal urinary free cortisol and postdexamethasone cortisol in social phobia: comparison to normal volunteers. *J Affect Disord* 1994; **30**: 155-161
102 **Lanzenberger R**, Wadsak W, Spindelegger C, Mitterhauser M, Akimova E, Mien LK, Fink M, Moser U, Savli M, Kranz GS, Hahn A, Kletter K, Kasper S. Cortisol plasma levels in social anxiety disorder patients correlate with serotonin-1A receptor binding in limbic brain regions. *Int J Neuropsychopharmacol* 2010; **13**: 1129-1143
103 **Levin AP**, Saoud JB, Strauman T, Gorman JM, Fyer AJ, Crawford R, Liebowitz MR. Responses of "generalized" and "discrete" socialphobics during publicspeaking. *J Anxiety Disord* 1993; **7**: 207-221
104 **Furlan PM**, DeMartinis N, Schweizer E, Rickels K, Lucki I. Abnormal salivary cortisol levels in social phobic patients in response to acute psychological but not physical stress. *Biol Psychiatry* 2001; **50**: 254-259
105 **Martel FL**, Hayward C, Lyons DM, Sanborn K, Varady S, Schatzberg AF. Salivary cortisol levels in socially phobic adolescent girls. *Depress Anxiety* 1999; **10**: 25-27
106 **van West D**, Claes S, Sulon J, Deboutte D. Hypothalamic-pituitary-adrenal reactivity in prepubertal children with social phobia. *J Affect Disord* 2008; **111**: 281-290
107 **Roelofs K**, van Peer J, Berretty E, Jong P, Spinhoven P, Elzinga BM. Hypothalamus-pituitary-adrenal axis hyperresponsiveness is associated with increased social avoidance behavior in social phobia. *Biol Psychiatry* 2009; **65**: 336-343
108 **Rettew DC**. Avoidant personality disorder, generalized social phobia, and shyness: putting the personality back into personality disorders. *Harv Rev Psychiatry* 2000; **8**: 283-297
109 **Schmidt LA**, Fox NA, Rubin KH, Sternberg EM, Gold PW, Smith CC, Schulkin J. Behavioral and neuroendocrine responses in shy children. *Dev Psychobiol* 1997; **30**: 127-140
110 **Brand S**, Wilhelm FH, Kossowsky J, Holsboer-Trachsler E, Schneider S. Children suffering from separation anxiety disorder (SAD) show increased HPA axis activity compared to healthy controls. *J Psychiatr Res* 2011; **45**: 452-459
111 **Kagan J**, Reznick JS, Snidman N. Biological bases of childhood shyness. *Science* 1988; **240**: 167-171
112 **Schweizer EE**, Swenson CM, Winokur A, Rickels K, Maislin G. The dexamethasone suppression test in generalised anxiety disorder. *Br J Psychiatry* 1986; **149**: 320-322
113 **Tiller JW**, Biddle N, Maguire KP, Davies BM. The dexamethasone suppression test and plasma dexamethasone in generalized anxiety disorder. *Biol Psychiatry* 1988; **23**: 261-270
114 **Mantella RC**, Butters MA, Amico JA, Mazumdar S, Rollman BL, Begley AE, Reynolds CF, Lenze EJ. Salivary cortisol is associated with diagnosis and severity of late-life generalized anxiety disorder. *Psychoneuroendocrinology* 2008; **33**: 773-781
115 **Tafet GE**, Feder DJ, Abulafia DP, Roffman SS. Regulation of hypothalamic-pituitary-adrenal activity in response to cognitive therapy in patients with generalized anxiety disorder. *Cogn Affect Behav Neurosci* 2005; **5**: 37-40
116 **Pomara N**, Willoughby LM, Sidtis JJ, Cooper TB, Greenblatt DJ. Cortisol response to diazepam: its relationship to age, dose, duration of treatment, and presence of generalized anxiety disorder. *Psychopharmacology* (Berl) 2005; **178**: 1-8
117 **Rosenbaum AH**, Schatzberg AF, Jost FA, Cross PD, Wells LA, Jiang NS, Maruta T. Urinary free cortisol levels in anxiety. *Psychosomatics* 1983; **24**: 835-837
118 **Steudte S**, Stalder T, Dettenborn L, Klumbies E, Foley P, Beesdo-Baum K, Kirschbaum C. Decreased hair cortisol concentrations in generalised anxiety disorder. *Psychiatry Res* 2011; **186**: 310-314

119 **Heim C**, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology* 2000; **25**: 1-35
120 **Fries E**, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. *Psychoneuroendocrinology* 2005; **30**: 1010-1016
121 **Henry JP**. Biological basis of the stress response. *Integr Physiol Behav Sci* 1992; **27**: 66-83
122 **Young EA**, Breslau N. Saliva cortisol in posttraumatic stress disorder: a community epidemiologic study. *Biol Psychiatry* 2004; **56**: 205-209
123 **Gunnar MR**, Vazquez DM. Low cortisol and a flattening of expected daytime rhythm: potential indices of risk in human development. *Dev Psychopathol* 2001; **13**: 515-538
124 **Greaves-Lord K**, Ferdinand RF, Oldehinkel AJ, Sondeijker FE, Ormel J, Verhulst FC. Higher cortisol awakening response in young adolescents with persistent anxiety problems. *Acta Psychiatr Scand* 2007; **116**: 137-144
125 **Joëls M**, Krugers H, Karst H. Stress-induced changes in hippocampal function. *Prog Brain Res* 2008; **167**: 3-15
126 **Meaney MJ**, Szyf M. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues Clin Neurosci* 2005; **7**: 103-123
127 **Weaver IC**, Meaney MJ, Szyf M. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proc Natl Acad Sci USA* 2006; **103**: 3480-3485

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