REVIEW

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HPA Axis Alterations in Mental Disorders: Impact on Memory and its Relevance for Therapeutic Interventions

Katja Wingenfeld[1] & Oliver T. Wolf[2]

1 Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf & Schön Klinik Hamburg-Eilbek, Germany
2 Department of Cognitive Psychology, Ruhr-University Bochum, Germany

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Correspondence
Oliver T. Wolf, Department of Cognitive Psychology, Ruhr-University Bochum, Universitätsstr. 150, D-44780 Bochum, Germany.
Tel.: +49-234-32-22670;
Fax: +49-234-32-14308;
E-mail: oliver.t.wolf@rub.de

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SUMMARY

Dysfunctions in hypothalamic–pituitary–adrenal (HPA) axis have been reported for several mental disorders that are also often characterized by memory disturbances. It is now well established that glucocorticoids influence cognitive processes by enhancing memory consolidation and impairing memory retrieval. There is further evidence for an association between HPA axis related disturbances and memory function in mental disorders. The present selective review provides a brief overview of HPA axis dysfunction and its impact on memory function in major depressive disorder, posttraumatic stress disorder, and borderline personality disorder. Furthermore, the relevance of these findings for therapeutic intervention is discussed.

Introduction

Following the biopsychosocial model of mental disorders, many studies have investigated the functioning of the hypothalamic–pituitary–adrenal (HPA) axis, which is an important part of the neuroendocrine system involved in the coordination of the stress response. Briefly, upon stress exposure, corticotropin-releasing factor (CRF) is released from the hypothalamus and is transported to the anterior pituitary, where it stimulates the secretion of adrenocorticotropin (ACTH), which in turn stimulates the synthesis and release of glucocorticoids (GCs) from the adrenal cortex. The neuroendocrine stress response is counter-regulated by circulating GCs via negative feedback mechanisms targeting the pituitary, hypothalamus, and hippocampus. This negative feedback loop is essential for the regulation of the HPA axis and, therefore, for the regulation of the stress response [1]. GCs mediate their effects by binding to two subtypes of intracellular receptors, the mineralocorticoid receptor (MR), and the glucocorticoid receptor (GR). These two receptors differ in their affinity and distribution within the CNS [2]. In addition, a membrane-bound MR has recently been characterized [3]. Because most of the effects associated with GCs–especially those that are related to the CNS–have been attributed to GR, we will focus here on this particular receptor type. GR have their highest density in the hippocampus [4] but are also prominent in the prefrontal cortex [5], which are both brain regions of substantial importance for memory function.

In healthy subjects, multiple previous investigations have found that acute administration of GCs impairs long-term memory retrieval [6–8]. Similar effects have been obtained using psychosocial laboratory stressors [9,10]. Memory consolidation, on the other hand, seems to be positively influenced by cortisol [7,11]. In addition, working memory is also impaired by GCs, whereas simple emotional learning (fear conditioning) as well as rigid stimulus response or habit learning is enhanced [5,12,13].

Several mental disorders are characterized by memory disturbances, which will be described later. These alterations are not just secondary symptoms but must be regarded as key features of these disorders. In major depressive disorder (MDD), memory disturbances are one of the symptoms defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and memory bias to negative information has been studied extensively [14]. In contrast, posttraumatic stress disorder (PTSD) is characterized by intense memories in which patients re-experience their traumatic experiences [15]. Furthermore, borderline personality disorder (BPD) is also characterized by neuropsychological disturbances [16], but comorbid axis I disorders might contribute to the clinical picture and perhaps explain some of the observed

neuropsychological deficits [17]. HPA axis dysregulations are not only a correlate of the these mental disorders but also predict symptom development [18,19], treatment resistance [20], and risk for suicide [21], which points to the importance of hormonal stress-regulation systems in psychopathology.

This review aims to integrate findings on the relationships between HPA axis and cognitive functioning (i.e., memory) in selected mental disorders, including MDD, PTSD, and BPD.

Major Depressive Disorder

MDD is one of the most prevalent mental disorders, with a 12-month prevalence rate of up to 10% [22]. A major depressive episode is characterized by depressed mood and/or loss of interest or pleasure accompanied by sleep disturbances, psychomotor agitation or retardation, fatigue and loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, as well as recurrent thoughts of death or suicide or even suicide attempt [23]. Biological, psychological, and social factors are known to play a role in the development of MDD, suggesting that depression results when a pre-existing vulnerability, or diathesis, is activated by stressful life events [24].

HPA Axis

Dysregulation of the HPA axis is a prominent finding in MDD. Several studies [25–29] but not all [26,30,31] found an enhanced basal and stimulated cortisol release in MDD. Furthermore, high cortisol levels after dexamethasone (DEX) administration (so-called Dex nonsuppression) has been reported in MDD [32], but again not all studies confirmed this effect [33]. These diverging findings might be due to differences in study populations, type of depression, and factors which are known to influence HPA axis, for example, psychotic versus nonpsychotic patients [31], melancholic versus atypical depression [34], comorbid anxiety [35], age [36], gender [37], and history of childhood trauma [24,38].

The finding of reduced feedback sensitivity has been interpreted as reflecting an exaggerated CRF drive [39] and/or as a reduction of functioning of GRs [40,41]. One of the most sensitive measurements of HPA axis feedback sensitivity is the combined DEX/CRF test. In that test, HPA axis activity is initially suppressed by dexamethasone treatment before exogenous CRF is given the following day. In depressed patients as well as in persons with childhood trauma, a pronounced escape from this suppression has been found with elevated ACTH and cortisol after CRF administration, further supporting the idea of reduced GR functioning [32]. In support of this hypothesis, post-mortem studies have reported a reduced GR mRNA in depressed patients [42]. Furthermore, an increased methylation of the GR gene promoter inhibiting GR expression [43] has been reported. GR gene polymorphisms are also discussed to be associated with depression [44,45]. Furthermore, recent findings suggest that single nucleotide polymorphisms of the GR gene, namely ER22/23EK, *Bcl*I, and 9beta A/G may be associated with an increased risk for major depression [29,30]. Traditionally, the GR has been at the focus of most studies examining neuroendocrine pathways to depression. However, recent evidence suggests that MR dysfunction might also play a role [2,46,47]. In light of the MR/GR balance model of depression [4], combined investigations of both receptors are now required.

The results of abnormal HPA axis functioning in patients with MDD have generally been interpreted as reflecting an exaggerated CRH drive and/or a reduced functioning of GRs. A possible shift of MR/GR balance seems to play an important role in this process [28]. Although it is still a matter of debate, GR and/or MR function and genetic variations of them appear to be important factors in the pathogenesis of MDD.

Memory

Memory disturbances are frequent in MDD. One of the most thoroughly investigated cognitive functions is hippocampal-based episodic/declarative memory. Cognitive performance in episodic memory tasks, including paragraph delayed recall, learning, and retrieval of word lists is impaired in MDD patients [48–50]. Disturbances in information processing, including a negative bias, is also prominent in MDD, although not all studies agree [51]. Furthermore, autobiographical memory seems to be less specific in these patients [52].

Surprisingly, only few studies have investigated the association between HPA axis functioning and memory performance in depression. Some studies found associations between cortisol levels and cognitive impairment in depressed patients [53–57], or predominantly in depressed patients with psychotic symptoms [58], but other studies failed to find such associations [59–63]. However, the cross-sectional and correlational design of these studies renders them inconclusive with regard to causal directionality.

To our knowledge, until recently only one study has investigated the effect of GC administration on memory in MDD [64]. Bremner et al. found that 2 days of 2 mg DEX treatment improved episodic memory in patients with MDD and suggested that a reduction of cortisol after DEX might have led to the observed memory improvement. In a recently published study by our working group, we investigated the effect of acute cortisol administration on autobiographic memory and found memory impairment in healthy subjects after cortisol intake [65]. In patients with MDD, no further reduction of autobiographical memory performance after cortisol could be observed but memory performance was worse compared to the control group (Figure 1). We hypothesized that the lack of an effect of acute cortisol administration on memory performance might be due to reduced functioning of hippocampal and/or prefrontal GRs. However, these two studies are not comparable with regard to the chosen GC (DEX vs. hydrocortisone) and with regard to the study design (repeated GC treatment vs. single treatment), which complicates the interpretation of these contrasting results.

Implication for Therapeutic Interventions

With respect to the treatment of depression, it has been shown that remission from depression is associated with normalization of HPA axis dysfunction. Impaired cortisol suppression, for example, is known to normalize after symptom improvement [32] but not within the depressive episode [66]. Thus, several pharmacological approaches aim to reduce HPA axis activity. Possible

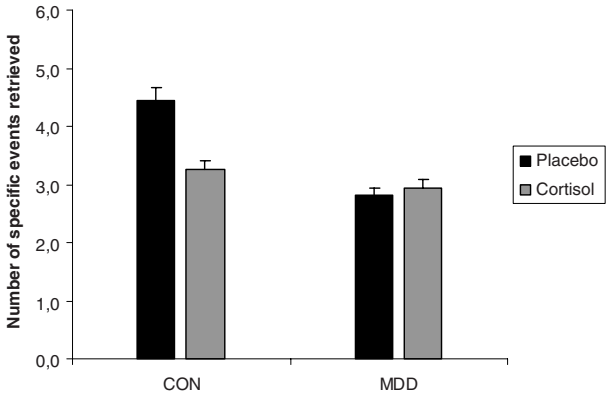

Figure 1 Autobiographic memory performance after 10 mg hydrocortisone and placebo. Evidence for reduced central glucocorticoid sensitivity in major depressive disorder (MDD). Although cortisol administration impaired autobiographic memory in healthy controls (n = 16), it had no effect on autobiographical memory in patients with MDD (n = 16). Taken from Schlosser et al. [65] with permission from Elsevier.

options are CRF and GR antagonists [67–71]. Alternatively, future approaches might target the MR or GR receptor (e.g., increasing the expression or sensitivity of the GR). To our knowledge, only one study has investigated the impact of antiglucocorticoids on cognitive function in mood disorder [72]. In this study, 20 patients with bipolar disorder were treated with mifepristone or placebo for 1 week. In contrast to placebo treatment, spatial working memory, verbal fluency, and spatial recognition memory improved significantly with mifepristone, irrespective of improvement in depressive symptoms. The improvement in cognition correlated inversely with basal cortisol levels. This suggests that initially impaired GC receptor function might be restored by the drug and a subsequently appropriate MR/GR balance might then account for the enhancement in cognitive performance. In addition, most antidepressants with known action on the serotonergic system influence HPA axis activity [73] because the HPA axis and the serotonergic system are interconnected [74,75]. Interestingly, citalopram, a selective serotonin reuptake inhibitor, has been shown not only to affect HPA axis and depression but also to improve working memory [76]. In another study, a 7 months treatment with an SSRI resulted in a significant improvement in memory function and a reduction in UFC excretion, but did not alter hippocampal volume [57]. Thus, it seems that antidepressants may improve hippocampal-mediated memory function without inducing structural changes.

Future treatment studies should assess HPA alterations as well as memory performances before and after treatment.

Posttraumatic Stress Disorder

PTSD follows exposure to a traumatic stressor, defined as a threat to the life of self or close other, associated with intense fear, horror, or helplessness. Traumatic experiences include childhood abuse, accident, rape, assault, war, and natural disaster. PTSD is characterized by three distinct but co-occurring symptoms: re-experiencing the trauma, avoidance, and hyperarousal [23]. The estimated lifetime prevalence of PTSD is 7.8% in the US population [77]. Stress-induced changes in neurobiological systems are believed to account for PTSD symptoms, such as an enhanced sensitization to stress, enhanced physiological arousal (i.e., hyperactivity of the noradrenergic system), and disturbances in learning and memory [78].

HPA Axis

In contrast to MDD, cortisol findings in PTSD suggest reduced rather than enhanced hormone concentrations [79–83]. However, these results are not uniformly consistent across all studies, and several factors, such as differences in trauma type, symptom patterns, gender, comorbidity with other mental disorders as well as genetic factors and other predisposing factors have been discussed to contribute to this inconsistency [83]. Furthermore, some studies suggest that comorbid depression plays an important role in HPA axis alteration in PTSD [84,85]. Beyond this so-called hypocortisolism, an enhanced suppression after a low dose (0.5 mg) of dexamethasone has been reported repeatedly [80]. This has been interpreted in the context of increased negative feedback regulation of the HPA axis due to increased GR binding [86,87]. Interestingly, in healthy subjects, enhanced suppression was found to be associated with higher levels of anxiety, interpersonal sensitivity, and avoidant coping strategies [88]. The lower dose of dexamethasone has been used because the standard dose of 1 mg almost completely suppresses cortisol secretion in normal people. To identify increases in negative feedback sensitivity, the dose of dexamethasone must be lowered to 0.5 mg, to avoid a floor effect and maximize distinctions between normal suppressors and hypersuppressors. Because of the fact that dexamethasone does not pass the blood–brain barrier and differs in pharmacokinetic and pharmacodynamic features from dexamethasone, a novel suppression test has been developed, that is, the prednisolone suppression test [89]. Further research in PTSD should, thus, move beyond the standard methods. At higher levels of the HPA axis, namely at the central nervous system, increased concentration of CRF has been found [78]. The finding of a blunted ATCH response to exogenous CRF, possibly due to down-regulation of pituitary CRF receptors, further supports the hypothesis of an enhanced activity of hypothalamic CRF [78].

Only few studies investigated prospectively the relationship between cortisol release and traumatization. These investigations found that lower cortisol measured shortly after the occurrence of a trauma was associated with the development of PTSD, suggesting that hypocortisolism might be a pre-existing risk factor that might lead to a maladaptive stress response [80]. Interestingly, the finding of a reduced hippocampal size [90], which has been formerly interpreted as result of enhanced cortisol release in response to the trauma, seems to be also a pre-existent risk factor as suggested by a twin study [91]. As mentioned earlier, the hippocampus is not only rich in GR but also important for memory, including autobiographical memory function. Of note, autobiographical memory is implicated in PTSD (e.g., in terms of intrusive memories).

Memory

Neuropsychological alterations are an important feature of the clinical presentation of PTSD. Several studies revealed problems with learning and memory, including deficits in verbal declarative memory functions and attention [92] as well as reduced autobiographical memory specificity and overgeneralized memory [93]. Patients with overgeneralized memory have difficulties in retrieving specific autobiographical events; instead, they tend to reply with abstract or general memory content (e.g., they summarize several different events) [94].

Studies that have investigated the effects of GC treatment on learning and memory in PTSD have yielded inconclusive results. One study reported a stronger negative effect of hydrocortisone on declarative memory in PTSD, compared to controls. Furthermore, in contrast to the control group patients showed impairments in working memory after pharmacological treatment [95]. In older PTSD patients, further evidence for a more pronounced effect of cortisol was obtained, but this time enhanced working memory performance after injection of hydrocortisone was observed [96]. Another study reported that hydrocortisone led to an impaired hippocampal-dependent trace eye-blink conditioning, which is a simple form of associative learning, only in PTSD patients but not in healthy control participants [97]. These findings are in line with the hypothesis of an enhanced GC sensitivity in these patients, which results in an exaggerated effect of GCs on neuropsychological functioning [47]. Contrary to these results, another study reported blunted effects of dexamethasone on declarative memory in PTSD [98]. However, in this experiment not only the pharmacological agent but also the treatment regime differed from the other studies, that is, dexamethasone was given for 2 days before memory testing.

With regard to PTSD symptoms, one might suggest that lower cortisol (in concert with an increased noradrenergic output) leads to a less well-integrated memory trace and integration of the traumatic event into autobiographical memory. Because cortisol is known to have inhibitory effects on memory retrieval, hypocortisolism might be associated with intrusive memories, flashbacks, and nightmares [13,79].

Implication for Therapeutic Interventions

Up to now only few studies have aimed to transfer neuroendocrine findings into treatment strategies. In one study, for example, patients were treated after cardiac surgery with hydrocortisone or standard therapy during the perioperative period. The authors found hydrocortisone treatment to be associated with a lower intensity of chronic stress and PTSD symptoms after 6 months [99] (Figure 2). This is in line with a former study of this group, in which the protecting effects of hydrocortisone during septic shock for the development of PTSD had been shown [100]. Thus, such a treatment immediately after the trauma might be an effective secondary-prevention strategy. In addition, in three patients with chronic PTSD, a reduction of symptoms has been reported after 10 mg/day cortisol over 1 month [101]. However, the results of this pilot study have yet to be replicated in a larger sample. Other intervention ideas, such as treatment with GR blocker, such as mifepristone, also need empirical support [102].

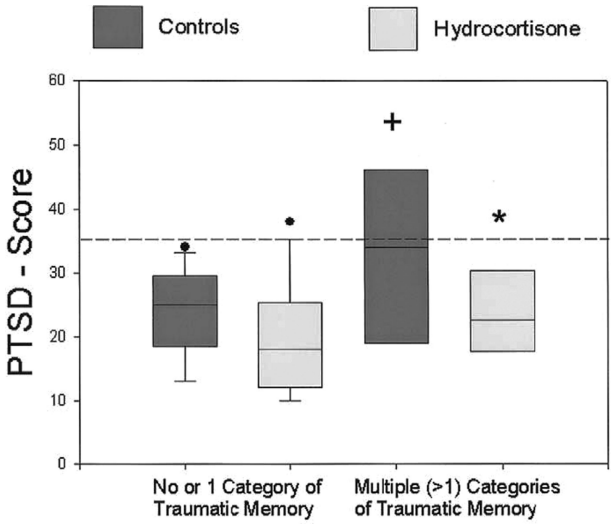

Figure 2 Posttraumatic stress disorder (PTSD) symptom scores in patients from the hydrocortisone group (N = 26) and patients from the control group (N = 22) with no or one category of traumatic memory and more than one category of traumatic memory, respectively. Evidence for the preventing effect of hydrocortisone treatment on PTSD symptoms. Taken from Schelling et al. [68] with permission from Elsevier. Note: The broken black line shows the 35-point cut-off value for PTSD diagnosis by the PTSD screening Questionnaire. Black dots indicate outliers. * indicates a significant reduction in PTSD scores in the hydrocortisone group (with multiple categories of traumatic memory) compared to the control group.

BPD: Psychopathology and Clinical Features

BPD is characterized by intense and rapidly changing mood states as well as by impulsivity, self-injurious behaviors, fear of abandonment, unstable relationships, and unstable self-image [23]. Patients with BPD often suffer from comorbid axis I disorders, with mood disorders (96.3%) and anxiety disorders (88.4%) being the most prominent [103].

Patients with BPD frequently report early, multiple, and chronic adverse or even traumatic experiences, such as repeated sexual or physical abuse or emotional or physical neglect, and it has been suggested that early life stress might be an important risk factor in the development of BPD [104].

HPA Axis

Most studies that investigated the HPA axis in BPD and used the 1 mg dexamethasone suppression test have yielded inconclusive results. However, most of these results suggested an association of reduced feedback inhibition with affective dysregulation or even with comorbid MDD [17]. In many of these studies, no formal diagnostic procedure (e.g., diagnostic interview, such as the SCID)

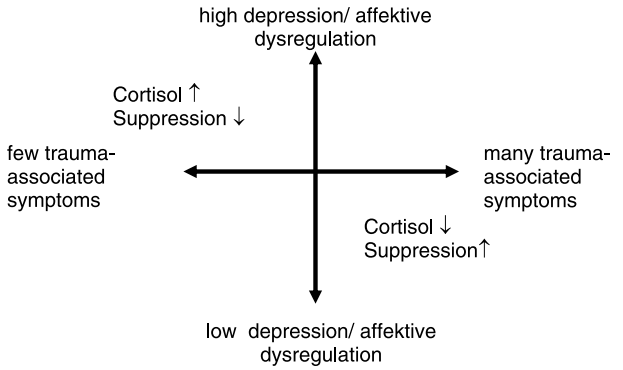

Figure 3 The association between HPA axis dysregulation (basal cortisol concentrations and suppression (feedback) after Dexamethasone application) and core psychopathology in BPD: two potential dimensions. Taken from Wingenfeld et al. [17], with permission from Elsevier.

was applied so that the data are difficult to interpret. More recent studies not only used more appropriate diagnostic procedures but some also used the low-dose DST to detect hyper-suppression. In sum, there is now evidence that comorbid disorders, such as MDD and PTSD, play an important role in terms of HPA feedback regulation in BPD [105,106].

Only a few studies so far have investigated basal cortisol release, suggesting enhanced cortisol concentrations [17]. Furthermore, an exaggerated ACTH and cortisol response in the combined DEX/CRF test has been found, but only among those who reported childhood abuse [106]. Again comorbid disorders, especially PTSD, seem to have an important influence on endocrine reactions [17]. Furthermore, dissociation, which is a prominent symptom in case of childhood trauma, has been shown to influence HPA axis functioning in BPD [107].

To conclude, studies investigating HPA axis functioning in BPD have provided compelling evidence for the impact of comorbid PTSD and depression on HPA axis feedback regulation in BPD (Figure 3). One might hypothesize that there are at least two subgroups of BPD patients with different endocrine patterns: one predominantly characterized by trauma-associated symptoms with unaltered to enhanced feedback sensitivity and normal to reduced cortisol release, and another subgroup with mood disturbances as core symptoms and HPA axis dysfunction in form of enhanced cortisol release and reduced feedback sensitivity [17].

Memory

Since the 1990s, increasing efforts have been made to characterize neuropsychological functioning of BPD patients. The majority of these studies aimed to determine neuropsychological functioning using standard tests and batteries with neutral stimuli. Although the results of many studies suggested a significant impairment concerning episodic memory functioning [16], other studies were unable to detect such deficits [108]. Interestingly, the pattern of results changed when emotional valence was also considered in more sophisticated experimental designs. The outcomes of many of these studies showed deficits among BPD patients regarding the control and inhibition of emotional interference. For example, one study reported an enhanced retrograde and anterograde amnesia in BPD patients in response to the presentation of stimuli with negative valence [109]. Using the directed forgetting task, a reduced inhibition of emotionally negative words in BPD patients has been documented [110]. Accordingly, a recent study also suggests no general impairment of verbal memory functions in BPD but found that control and inhibition of interference of emotionally significant material seem to be disturbed [111]. Furthermore, comorbid disorders, such as PTSD seem to play an important role in explaining the attentional bias found in these patients [112].

The findings of impairments in the control and inhibition of emotionally negative information might be interpreted in light of psychobiological research. Neuroimaging studies have revealed evidence for a hyperactive responsiveness of the amygdala in response to emotional stimuli and a reduced size of the ACC and hippocampus in BPD. Thus, a dysfunctional network of brain regions that are involved in the regulation of emotions and response inhibition might underlie these effects [17].

Although memory dysfunctions and HPA dysregulation are prominent in BPD, these associations have attracted little scientific attention. For example, there is not a single study published as of today that investigated the effects of cortisol administration on cognition in BPD. Thus, studies that integrate neuroendocrinology and neuropsychology are urgently needed.

Implications for Therapeutic Interventions

Because of the equivocal findings of HPA axis regulation in BPD, attempts to study pharmacological treatment strategies in this field are rare. However, there is evidence that the use of serotonin reuptake inhibitors, that is, fluvoxamine, may regulate the hyperresponsiveness of the HPA axis in BPD patients [113], especially in those patients who reported childhood abuse. Interestingly, the magnitude of the reduction was not dependent on the presence of comorbid PTSD and depression. This kind of research approach holds promise to integrate endocrine and clinical approaches of BPD. Another study has investigated the effects of carbamazepin on HPA axis in BPD, which is not only used in the treatment of epilepsy but also of affective disorders, and found increased post-dexamethasone plasma cortisol values [114]. However, the underlying mechanisms as well as the clinical benefit are still under discussion.

Summary and Conclusions

There is compelling evidence that stress and GCs affect learning and memory, with impairing effects on memory retrieval and enhancing effects on memory consolidation [115]. Several mental disorders are characterized by dysfunctions of the HPA axis as well as memory disturbances, which might be associated with each other. Thus, recent research has aimed to transfer neuroendocrine findings into treatment strategies. In PTSD, for example, there is some evidence that GC administration might reduce the retrieval of aversive memories [116], but more research is needed to draw final conclusions about effectiveness and underlying mechanisms.

In major depression, much effort is currently being directed at the development of pharmacological agents that may normalize HPA axis activity, with CRF and GR antagonists being of particularly great interest [68,69]. Of note, there is evidence for subgroups, with different findings on HPA axis regulation not only in BPD [17] but also in depression, as found by the studies of Heim [24], suggesting an important impact of early trauma on HPA axis functioning. Furthermore, it seems that different treatment strategies might be needed for patients with and without trauma, with psychotherapeutic strategies being of great importance [117]. Thus, an enhanced recognition of interindividual differences appears indicated. Accordingly, the development of new treatment strategies should take these findings into account to provide a more individually tailored therapy.

The HPA axis is not an isolated system in the regulation of the stress response. There is a close association between the locus coeruleus-noradrenergic system and HPA axis [118]. Together they interact at multiple levels in the periphery and the brain and influence memory function [13]. Several brain regions are involved in these processes, such as, for example, the amygdale and hippocampus as well as prefrontal and temporal areas [119]. The locus coeruleus-noradrenergic system is especially important in the context of emotional memory and conditioning. There is evidence that noradrenergic activation leads to enhanced memory consolidation as well as enhanced fear conditioning but reduced extinction [119–121]. Interestingly, adrenergic activation seems to mediate the effects of GC on memory [122–124]. In fact, the disorders discussed earlier are characterized not only by alterations in emotional memory, learning and information processing but also by disturbances in locus coeruleus-noradrenergic system as well as dysfunctions in related brain areas [17,125–129]. Up to now, clinical studies that investigate the interaction between locus coeruleus-noradrenergic system and HPA axis and its association with memory in mental disorders are rare. However, in major depression, there is first evidence for a disturbed interaction between these systems [125,130].

Another important neurotransmitter system in this context is the serotonergic system. In MDD as well as BPD, dysfunctions of the serotonergic system have been reported repeatedly, including reduced $5HT_{1A}$ receptor binding in the medial prefrontal cortex, amygdala and hippocampus, or lower cortisol and prolactine responses to *meta*-chlorophenylpiperazine [17,131,132]. There are strong interconnections among the hippocampus, stress response, and the serotonergic system [133]. Interestingly, in BPD, frontal brain regions as well as parts of the limbic system seem to be associated with dysregulation of the serotonergic system. Symptoms of impulsivity, aggression, and suicidal behavior seem to be strongly mediated by the serotonergic system and are prominent features in patients with BPD [132]. Furthermore, fluvoxamine treatment has been found to reduce the hyperresponsiveness of the HPA axis in BPD patients, especially in those with a history of sustained childhood abuse [134]. Serotonin also mediates the effects of stress on hippocampal GR expression [135,136]. One might hypothesize that stress-related alteration of HPA axis regulation in concert with diminished serotonergic functioning may contribute to change in brain structure and metabolism in the disorders discussed here.

Results from neuroimaging studies might help to better understand the set of presented findings. For depressive disorders, Drevets et al. have suggested that an extended "visceromotor network," including orbital and prefrontal brain regions interfere with those systems that modulate emotional behavior [137]. In fact, an increased activation of the amygdala as well as a reduced activation of the cingulate gyrus and reduced hippocampal volume has been reported for MDD patients [138,139]. Interestingly, deficits to activate hippocampus and anterior cingulate cortex (ACC) during a verbal memory encoding task have been demonstrated in patients with MDD [140]. However, these findings are not specific for depression. In BPD, a reduced hippocampal size has been also reported as well as volume reductions in the ACC and the amygdala. Accordingly, functional imaging studies have found a decreased activation in these regions, except for the amygdala, where enhanced activation has typically been reported [17]. Furthermore, prefronatal areas are also involved, which leads to the assumption of a disturbed fronto-limbic network in BPD [141], which shows some concordance with those brain region which seem to be involved in MDD. In PTSD, were most HPA axis finding are contrary to those found in MDD and BPD, neuroimaging studies also revealed evidence of dysfunctions in the hippocampus (mostly reduced size and activity) and the amygdala (enhanced activity). Furthermore, prefrontal regions as well as the ACC seem to play an important role [128]. However, on the central level of the HPA axis, that is, CRF release, PTSD is also characterized by an enhanced activation, which has also been suggested for MDD [142]. Possibly, the finding of hypocortisolism at the periphery might be an adaptation to a chronically activated HPA axis.

As mentioned previously, the hippocampus plays an important role in memory function and has a high density of GR. Therefore, it is thought to be a stress-sensitive brain region and, thus, sensitive for the damaging effects of stress and GCs [133]. Repeated stress seems to result, for example, in a disruption of neurogenesis and dendritic atrophy of the hippocampus [143]. However, whether these alterations have to be interpreted as a consequence of GC exposure or have to be understood as a pre-existing risk factor is still a matter of debate [144]. Other brain regions also seem to be negatively influenced by chronic stress (e.g., the prefrontal cortex). In contrast chronic stress has been found to increase dendritic growth in the amygdala, which seems to be associated with greater anxiety [145,146]. These observations fit with clinical studies suggesting enhanced amygdala activation in several mental disorders, such as PTSD or BPD.

In sum, the mental disorders discussed here appear to be characterized by distinct patterns of dysregulation in stress regulation systems, with similarities at central levels of the HPA axis but, in part, distinctions at the periphery. Furthermore, they show several cognitive impairments, with memory disturbances being prominent and part of the diagnostic criteria. The discussed alterations in several brain regions, which can be described in simplified fashion as disturbed fronto-limbic networks, might contribute to these memory problems. Possibly, stress hormones are one reason for neural alterations, such as atrophy of specific brain regions. Furthermore, stress hormones have a direct impact on memory function and, thus, may be directly associated with related memory

disturbances in mental disorders. Within the last years, novel approaches in pharmacotherapy and psychotherapy have emerged. There is some evidence, for example, that antiglucocorticoids have an antidepressant effect, but controlled trials are needed. Furthermore, there is also preliminary evidence that HPA axis dysfunction in MDD patients can be altered via psychotherapy [147]. This is of importance for patients who are known to respond less to pharmacotherapy, that is, MDD patients with a history of early trauma [117]. Studies in healthy human subjects indicate that the effect is partly mediated by the anticipatory appraisal of the stressor. Evidently, the relationship between GCs and cognition is not one-sided but reciprocal. Future studies in patient populations including measures of HPA axis and cognitive function are needed to replicate the preliminary positive results in the treatment of cognitive impairment with either pharmacotherapy or psychotherapy. Furthermore, more integrative research is needed, which combines, for example, endocrine and imaging methods, focussing on the dynamic interplay of GCs with brain structures involved in cognitive performance.

Conflicts of Interest

The authors declare no conflict of interests.

References

1. Carrasco GA, Van de Kar LD. Neuroendocrine pharmacology of stress. *Eur J Pharmacol* 2003;**463**:235–272.
2. de Kloet ER, Joels M, Holsboer F. Stress and the brain: From adaptation to disease. *Nat Rev* 2005;**6**:463–475.
3. Joels M, Karst H, DeRijk R, de Kloet ER. The coming out of the brain mineralocorticoid receptor. *Trends Neurosci* 2008;**31**:1–7.
4. de Kloet ER. Hormones, brain and stress. *Endocr Regul* 2003;**37**:51–68.
5. Lupien SJ, Lepage M. Stress, memory, and the hippocampus: Can't live with it, can't live without it. *Behav Brain Res* 2001;**127**:137–158.
6. Buchanan TW. Retrieval of emotional memories. *Psychol Bull* 2007;**133**:761–779.
7. Roozendaal B. Stress and memory: Opposing effects of glucocorticoids on memory consolidation and memory retrieval. *Neurobiol Learn Mem* 2002;**78**:578–595.
8. Het S, Ramlow G, Wolf OT. A meta-analytic review of the effects of acute cortisol administration on human memory. *Psychoneuroendocrinology* 2005;**30**:771–784.
9. Elzinga BM, Bakker A, Bremner JD. Stress-induced cortisol elevations are associated with impaired delayed, but not immediate recall. *Psychiatry Res* 2005;**134**:211–223.
10. Kuhlmann S, Piel M, Wolf OT. Impaired memory retrieval after psychosocial stress in healthy young men. *J Neurosci* 2005;**25**:2977–2982.
11. Wolf OT. Stress and memory in humans: Twelve years of progress? *Brain Res* 2009;**1293**:142–154.
12. Schwabe L, Wolf OT, Oitzl MS. Memory formation under stress: quantity and quality. *Neurosci Biobehav Rev* 2010;**34**:584–591.
13. Wolf OT. The influence of stress hormones on emotional memory: Relevance for psychopathology. *Acta Psychol* 2008;**127**:513–531.
14. Leppanen JM. Emotional information processing in mood disorders: A review of behavioral and neuroimaging findings. *Curr Opin Psychiatry* 2006;**19**:34–39.
15. Nemeroff CB, Bremner JD, Foa EB, Mayberg HS, North CS, Stein MB. Posttraumatic stress disorder: A state-of-the-science review. *J Psychiatric Res* 2006;**40**:1–21.
16. Ruocco AC. The neuropsychology of borderline personality disorder: A meta-analysis and review. *Psychiatry Res* 2005;**137**:191–202.
17. Wingenfeld K, Spitzer C, Rullkotter N, Lowe B. Borderline personality disorder: Hypothalamus pituitary adrenal axis and findings from neuroimaging studies. *Psychoneuroendocrinology* 2010;**35**:154–170.
18. Mannie ZN, Harmer CJ, Cowen PJ. Increased waking salivary cortisol levels in young people at familial risk of depression. *Am J Psychiatry* 2007;**164**:617–621.
19. Goodyer IM, Herbert J, Tamplin A. Psychoendocrine antecedents of persistent first-episode major depression in adolescents: A community-based longitudinal enquiry. *Psychol Med* 2003;**33**:601–610.
20. Juruena MF, Pariante CM, Papadopoulos AS, Poon L, Lightman S, Cleare AJ. Prednisolone suppression test in depression: Prospective study of the role of HPA axis dysfunction in treatment resistance. *Br J Psychiatry* 2009;**194**:342–349.
21. Markianos M, Tripodianakis J, Istikoglou C, et al. Suicide attempt by jumping: A study of gonadal axis hormones in male suicide attempters versus men who fell by accident. *Psychiatry Res* 2009;**170**:82–85.
22. 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.
23. Widiger TA, Frances AJ, Pincus HA, et al., editors. *Diagnostic and statistical manual of mental disorders (DSM-IV)*. Sourcebook, **Vol. 4**. Washington, DC: American Psychiatric Association, 1998.
24. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology* 2008;**33**:693–710.
25. Bhagwagar Z, Hafizi S, Cowen PJ. Increased salivary cortisol after waking in depression. *Psychopharmacology (Berl)* 2005;**182**:54–57.
26. Strickland PL, Deakin JF, Percival C, Dixon J, Gater RA, Goldberg DP. Bio-social origins of depression in the community. Interactions between social adversity, cortisol and serotonin neurotransmission. *Br J Psychiatry* 2002;**180**:168–173.
27. Deuschle M, Schweiger N, Weber B, et al. Diurnal activity and pulsatility of the hypothalamus-pituitary-adrenal system in male depressed patients and healthy controls. *J Clin Endocrinol Metab* 1997;**82**:234–238.
28. Vreeburg SA, Hoogendijk WJ , vanPelt J, et al. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: Results from a large cohort study. *Arch Gen Psychiatry* 2009;**66**:617–626.
29. Burke HM, Davis MC, Otte C, Mohr DC. Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology* 2005;**30**:846–856.
30. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low CRH/NE states. *Mol Psychiatry* 2002;**7**:254–275.
31. Posener JA, DeBattista C, Williams GH, Chmura Kraemer H, Kalehzan BM, Schatzberg AF. 24-Hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression. *Arch Gen Psychiatry* 2000;**57**:755–760.
32. Ising M, Kunzel HE, Binder EB, Nickel T, Modell S, Holsboer F. The combined dexamethasone/CRH test as a potential surrogate marker in depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2005;**29**:1085–1093.
33. Posener JA, DeBattista C, Williams GH, Schatzberg AF. Cortisol feedback during the HPA quiescent period in patients with major depression. *Am J Psychiatry* 2001;**158**:2083–2085.
34. Gold PW, Gabry KE, Yasuda MR, Chrousos GP. Divergent endocrine abnormalities in melancholic and atypical depression: Clinical and pathophysiologic implications. *Endocrinol Metab Clin North Am* 2002;**31**:37–62, vi.
35. Young EA, Abelson JL, Cameron OG. Effect of comorbid anxiety disorders on the hypothalamic-pituitary-adrenal axis response to a social stressor in major depression. *Biol Psychiatry* 2004;**56**:113–120.
36. Bremmer MA, Deeg DJ, Beekman AT, Penninx BW, Lips P, Hoogendijk WJ. Major depression in late life is associated with both hypo- and hypercortisolemia. *Biol Psychiatry* 2007;**62**:479–486.
37. Chopra KK, Ravindran A, Kennedy SH, et al. Sex differences in hormonal responses to a social stressor in chronic major depression. *Psychoneuroendocrinology* 2009;**34**:1235–1241.
38. 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.
39. Nemeroff CB. The corticotropin-releasing factor (CRF) hypothesis of depression: New findings and new directions. *Mol Psychiatry* 1996;**1**:336–342.
40. Pariante CM, Miller AH. Glucocorticoid receptors in major depression: Relevance to pathophysiology and treatment. *Biol Psychiatry* 2001;**49**:391–404.
41. Holsboer F. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 2000;**23**: 477–501.
42. Webster MJ, Knable MB, O'Grady J, Orthmann J, Weickert CS. Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. *Mol Psychiatry* 2002;**7**:985–994, 24.
43. McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009;**12**:342–348.
44. Otte C, Wust S, Zhao S, Pawlikowska L, Kwok PY, Whooley MA. Glucocorticoid receptor gene and depression in patients with coronary heart disease: The Heart and Soul Study-2009 Curt Richter Award Winner. *Psychoneuroendocrinology* 2009;**34**:1574–1581.
45. Binder EB, Salyakina D, Lichtner P, et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet* 2004;**36**:1319–1325.
46. Otte C, Hinkelmann K, Moritz S, et al. Modulation of the mineralocorticoid receptor as add-on treatment in depression: A randomized, double-blind, placebo-controlled proof-of-concept study. *J Psychiatr Res* 2010;**44**:339–346.
47. Rohleder N, Wolf JM, Wolf OT. Glucocorticoid sensitivity of cognitive and inflammatory processes in depression and posttraumatic stress disorder. *Neurosci Biobehav Rev* 2010;**35**:104–114.

48. Chamberlain SR, Sahakian BJ. The neuropsychology of mood disorders. *Curr Psychiatry Rep* 2006;**8**:458–463.
49. Veiel HO. A preliminary profile of neuropsychological deficits associated with major depression. *J Clin Exp Neuropsychol* 1997;**19**:587–603.
50. Porter RJ, Bourke C, Gallagher P. Neuropsychological impairment in major depression: Its nature, origin and clinical significance. *Aust N Z J Psychiatry* 2007;**41**:115–128.
51. Williams JM, Mathews A, MacLeod C. The emotional Stroop task and psychopathology. *Psychol Bull* 1996;**120**:3–24.
52. Van Vreeswijk MF, De Wilde EJ. Autobiographical memory specificity, psychopathology, depressed mood and the use of the Autobiographical Memory Test: A meta-analysis. *Behav Res Ther* 2004;**42**:731–743.
53. Rubinow DR, Post RM, Savard R, Gold PW. Cortisol hypersecretion and cognitive impairment in depression. *Arch Gen Psychiatry* 1984;**41**:279–283.
54. Egeland J, Lund A, Landro NI, et al. Cortisol level predicts executive and memory function in depression, symptom level predicts psychomotor speed. *Acta Psychiatr Scand* 2005;**112**:434–441.
55. Hinkelmann K, Moritz S, Botzenhardt J, et al. Cognitive impairment in major depression: Association with salivary cortisol. *Biol Psychiatry* 2009;**66**:879–885.
56. Gomez RG, Posener JA, Keller J, Debattista C, Solvason B, Schatzberg AF. Effects of major depression diagnosis and cortisol levels on indices of neurocognitive function. *PNEC* 2009;**34**:1012–1018.
57. Vythilingam M, Vermetten E, Anderson GM, et al. Hippocampal volume, memory, and cortisol status in major depressive disorder: Effects of treatment. *Biol Psychiatry* 2004;**56**:101–112.
58. Gomez RG, Fleming SH, Keller J, et al. The neuropsychological profile of psychotic major depression and its relation to cortisol. *Biol Psychiatry* 2006;**60**:472–478.
59. O'Brien JT, Lloyd A, McKeith I, Gholkar A, Ferrier N. A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *Am J Psychiatry* 2004;**161**:2081–2090.
60. Zobel AW, Nickel T, Sonntag A, Uhr M, Holsboer F, Ising M. Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. a prospective study. *J Psychiatric Res* 2001;**35**:83–94.
61. Reppermund S, Zihl J, Lucae S, et al. Persistent cognitive impairment in depression: The role of psychopathology and altered hypothalamic-pituitary-adrenocortical (HPA) system regulation. *Biol Psychiatry* 2007;**62**:400–406.
62. Adler G, Jajcevic A. Post-dexamethasone cortisol level and memory performance in elderly depressed patients. *Neurosci Lett* 2001;**298**:142–144.
63. Van Londen L, Goekoop JG, Zwinderman AH, Lanser JB, Wiegant VM, De Wied D. Neuropsychological performance and plasma cortisol, arginine vasopressin and oxytocin in patients with major depression. *Psychol Med* 1998;**28**:275–284.
64. Bremner JD, Vythilingam M, Vermetten E, Anderson G, Newcomer JW, Charney DS. Effects of glucocorticoids on declarative memory function in major depression. *Biol Psychiatry* 2004;**55**:811–815.
65. Schlosser N, Wolf OT, Fernando SC, et al. Effects of acute cortisol administration on autobiographical memory in patients with major depression and healthy controls. *Psychoneuroendocrinology* 2010;**35**:316–320.
66. Charles G, Wilmotte J, Quenon M, Mendlewicz J. Reproducibility of the dexamethasone suppression test in depression. *Biol Psychiatry* 1982;**17**:845–848.
67. Gallagher P, Reid KS, Ferrier IN. Neuropsychological functioning in health and mood disorder: Modulation by glucocorticoids and their receptors. *PNEC* 2009;**34**(Suppl. 1):196–207.
68. Berton O, Nestler EJ. New approaches to antidepressant drug discovery: Beyond monoamines. *Nat Rev* 2006;**7**: 137–151.
69. Schule C, Baghai TC, Eser D, Rupprecht R. Hypothalamic-pituitary-adrenocortical system dysregulation and new treatment strategies in depression. *Expert Rev Neurotherapeutics* 2009;**9**:1005–1019.
70. Wulsin AC, Herman JP, Solomon MB. Mifepristone decreases depression-like behavior and modulates neuroendocrine and central hypothalamic-pituitary-adrenocortical axis responsiveness to stress. *PNEC* 2010;**35**:1100–1112.
71. Nikisch G. Involvement and role of antidepressant drugs of the hypothalamic-pituitary-adrenal axis and glucocorticoid receptor function. *Neuro Endocrinol Lett* 2009;**30**:11–16.
72. Young AH, Gallagher P, Watson S, Del-Estal D, Owen BM, Ferrier IN. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology* 2004;**29**:1538–1545.
73. Pariante CM, Thomas SA, Lovestone S, Makoff A, Kerwin RW. Do antidepressants regulate how cortisol affects the brain ? *Psychoneuroendocrinology* 2004;**29**:423–447.
74. Porter RJ, Gallagher P, Watson S, Young AH. Corticosteroid-serotonin interactions in depression: A review of the human evidence. *Psychopharmacology (Berl)* 2004;**173**:1–17.
75. Marcos B, Aisa B, Ramirez MJ. Functional interaction between 5-HT(6) receptors and hypothalamic-pituitary-adrenal axis: Cognitive implications. *Neuropharmacology* 2008;**54**:708–714.
76. Zobel AW, Schulze-Rauschenbach S , vonWiddern OC, et al. Improvement of working but not declarative memory is correlated with HPA normalization during antidepressant treatment. *J Psychiatric Res* 2004;**38**:377–383.
77. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 1995;**52**:1048–1060.
78. Heim C, Nemeroff CB. Neurobiology of posttraumatic stress disorder. *CNS Spectrums* 2009;**14**:13–24.
79. Yehuda R. Status of glucocorticoid alterations in post-traumatic stress disorder. *Ann N Y Acad Sci* 2009;**1179**:56–69.
80. Yehuda R. Current status of cortisol findings in post-traumatic stress disorder. *Psychiatr Clin North Am* 2002;**25**:341–368, vii.
81. 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 Psychiatric Res* 2006;**40**:550–567.
82. Olff M, Guzelcan Y, de Vries GJ, Assies J, Gersons BP. HPA- and HPT-axis alterations in chronic posttraumatic stress disorder. *Psychoneuroendocrinology* 2006;**31**:1220–1230.
83. Meewisse ML, Reitsma JB, de Vries GJ, Gersons BP, Olff M. Cortisol and post-traumatic stress disorder in adults: Systematic review and meta-analysis. *Br J Psychiatry* 2007;**191**:387–392.
84. de Kloet C, Vermetten E, Lentjes E, et al. Differences in the response to the combined DEX-CRH test between PTSD patients with and without co-morbid depressive disorder. *Psychoneuroendocrinology* 2008;**33**:313–320.
85. Vythilingam M, Gill JM, Luckenbaugh DA, et al. Low early morning plasma cortisol in posttraumatic stress disorder is associated with co-morbid depression but not with enhanced glucocorticoid feedback inhibition. *Psychoneuroendocrinology* 2010;**35**:442–450.
86. Yehuda R, Golier JA, Yang RK, Tischler L. Enhanced sensitivity to glucocorticoids in peripheral mononuclear leukocytes in posttraumatic stress disorder. *Biol Psychiatry* 2004;**55**:1110–1116.
87. Rohleder N, Joksimovic L, Wolf JM, Kirschbaum C. Hypocortisolism and increased glucocorticoid sensitivity of pro-Inflammatory cytokine production in Bosnian war refugees with posttraumatic stress disorder. *Biol Psychiatry* 2004;**55**:745–751.
88. Hori H, Ozeki Y, Teraishi T, et al. Relationships between psychological distress, coping styles, and HPA axis reactivity in healthy adults. *J Psychiatr Res* 2010;**44**:865–873.
89. Pariante CM, Papadopoulos AS, Poon L, et al. A novel prednisolone suppression test for the hypothalamic-pituitary-adrenal axis. *Biol Psychiatry* 2002;**51**:922–930.
90. Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci Biobehav Rev* 2006;**30**:1004–1031.
91. Gilbertson MW, Shenton ME, Ciszewski A, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci* 2002;**5**:1242–1247.
92. Golier J, Yehuda R. Neuropsychological processes in post-traumatic stress disorder. *Psychiatr Clin North Am* 2002;**25**:295–315, vi.
93. Buckley TC, Blanchard EB, Neill WT. Information processing and PTSD: A review of the empirical literature. *Clin Psychol Rev* 2000;**20**:1041–1065.
94. Schonfeld S, Ehlers A. Overgeneral memory extends to pictorial retrieval cues and correlates with cognitive features in posttraumatic stress disorder. Emotion (Washington, DC). 2006;**6**:611–621.
95. Grossman R, Yehuda R, Golier J, McEwen B, Harvey P, Maria NS. Cognitive effects of intravenous hydrocortisone in subjects with PTSD and healthy control subjects. *Ann N Y Acad Sci* 2006;**1071**:410–421.
96. Yehuda R, Harvey PD, Buchsbaum M, Tischler L, Schmeidler J. Enhanced effects of cortisol administration on episodic and working memory in aging veterans with PTSD. *Neuropsychopharmacology* 2007;**32**:2581–2591.
97. Vythilingam M, Lawley M, Collin C, et al. Hydrocortisone impairs hippocampal-dependent trace eyeblink conditioning in post-traumatic stress disorder. *Neuropsychopharmacology* 2006;**31**:182–188.
98. Bremner JD, Vythilingam M, Vermetten E, et al. Effects of dexamethasone on declarative memory function in posttraumatic stress disorder. *Psychiatry Res* 2004;**129**:1–10.
99. Schelling G, Kilger E, Roozendaal B, et al. Stress doses of hydrocortisone, traumatic memories, and symptoms of posttraumatic stress disorder in patients after cardiac surgery: A randomized study. *Biol Psychiatry* 2004;**55**:627–633.
100. Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhausler HB, Kapfhammer HP. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. *Biol Psychiatry* 2001;**50**:978–985.
101. Aerni A, Traber R, Hock C, et al. Low-dose cortisol for symptoms of posttraumatic stress disorder. *Am J Psychiatry* 2004;**161**:1488–1490.
102. Yehuda R, Golier J. Is there a rationale for cortisol-based treatments for PTSD ? *Expert Rev Neurotherapeutics* 2009;**9**:1113–1115.
103. Zanarini MC, Frankenburg FR, Dubo ED, et al. Axis I comorbidity of borderline personality disorder. *Am J Psychiatry* 1998;**155**: 1733–1739.
104. McLean LM, Gallop R. Implications of childhood sexual abuse for adult borderline personality disorder and complex posttraumatic stress disorder. *Am J Psychiatry* 2003;**160**:369–371.
105. Wingenfeld K, Hill A, Adam B, Driessen M. Dexamethasone suppression test in borderline personality disorder: Impact of PTSD symptoms. *Psychiatry Clin Neurosci* 2007;**61**:681–683.

106. Rinne T, de Kloet ER, Wouters L, Goekoop JG, DeRijk RH, Van Den Brink W. Hyperresponsiveness of hypothalamic-pituitary-adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. *Biol Psychiatry* 2002;**52**:1102–1112.
107. Simeon D, Knutelska M, Smith L, Baker BR, Hollander E. A preliminary study of cortisol and norepinephrine reactivity to psychosocial stress in borderline personality disorder with high and low dissociation. *Psychiatry Res* 2007;**149**:177–184.
108. Beblo T, Saavedra AS, Mensebach C, et al. Deficits in visual functions and neuropsychological inconsistency in Borderline Personality Disorder. *Psychiatry Res* 2006;**145**:127–135.
109. Hurlemann R, Hawellek B, Maier W, Dolan RJ. Enhanced emotion-induced amnesia in borderline personality disorder. *Psychol Med* 2007;**37**:971–981.
110. Domes G, Winter B, Schnell K, Vohs K, Fast K, Herpertz SC. The influence of emotions on inhibitory functioning in borderline personality disorder. *Psychol Med* 2006;**36**:1163–1172.
111. Mensebach C, Wingenfeld K, Driessen M, et al. Emotion-induced memory dysfunction in borderline personality disorder. *Cognitive Neuropsychiatry* 2009;**14**:524–541.
112. Wingenfeld K, Mensebach C, Rullkoetter N, et al. Attentional bias to personally relevant words in borderline personality disorder is strongly related to comorbid posttraumatic stress disorder. *J Pers Disord* 2009;**23**:141–155.
113. Rinne T, Van Den Brink W, Wouters L, van Dyck R. SSRI treatment of borderline personality disorder: A randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. *Am J Psychiatry* 2002;**159**:2048–2054.
114. De la Fuente JM, Bobes J, Vizuete C, Mendlewicz J. Effects of carbamazepine on dexamethasone suppression and sleep electroencephalography in borderline personality disorder. *Neuropsychobiology* 2002;**45**:113–119.
115. Wolf OT. HPA axis and memory. *Best Pract Res Clin Endocrinol Metab* 2003;**17**:287–299.
116. de Quervain DJ, Aerni A, Schelling G, Roozendaal B. Glucocorticoids and the regulation of memory in health and disease. *Frontiers in Neuroendocrinology*. 2009;**30**:358–370.
117. Nemeroff CB, Heim CM, Thase ME, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci USA* 2003;**100**:14293–14296.
118. Pacak K, Palkovits M. Stressor specificity of central neuroendocrine responses: Implications for stress-related disorders. *Endocr Rev* 2001;**22**:502–548.
119. LaBar KS, Cabeza R. Cognitive neuroscience of emotional memory. *Nat Rev* 2006;**7**:54–64.
120. Debiec J, Ledoux JE. Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. *Neuroscience* 2004;**129**:267–272.
121. Cahill L, Babinsky R, Markowitsch HJ, McGaugh JL. The amygdala and emotional memory. *Nature* 1995;**377**:295–296.
122. Roozendaal B, Hui GK, Hui IR, Berlau DJ, McGaugh JL, Weinberger NM. Basolateral amygdala noradrenergic activity mediates corticosterone-induced enhancement of auditory fear conditioning. *Neurobiol Learn Mem* 2006;**86**:249–255.
123. Elzinga BM, Roelofs K. Cortisol-induced impairments of working memory require acute sympathetic activation. *Behav Neurosci* 2005;**119**:98–103.
124. van Stegeren AH, Wolf OT, Everaerd W, Scheltens P, Barkhof F, Rombouts SA. Endogenous cortisol level interacts with noradrenergic activation in the human amygdala. *Neurobiol Learn Mem* 2007;**87**:57–66.
125. Wong ML, Kling MA, Munson PJ, et al. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: Relation to hypercortisolism and corticotropin-releasing hormone. *Proc Natl Acad Sci USA* 2000;**97**:325–330.
126. Ebner-Priemer UW, Badeck S, Beckmann C, et al. Affective dysregulation and dissociative experience in female patients with borderline personality disorder: A startle response study. *J Psychiatric Res* 2005;**39**:85–92.
127. Southwick SM, Bremner JD, Rasmusson A, Morgan CA, 3rd, Arnsten A, Charney DS. Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biol Psychiatry* 1999;**46**:1192–1204.
128. Bremner JD. Neuroimaging in posttraumatic stress disorder and other stress-related disorders. *Neuroimaging Clin N Am* 2007;**17**:523–538, ix.
129. Mayberg HS. Limbic-cortical dysregulation: A proposed model of depression. *J Neuropsychiatry Clin Neurosci* 1997;**9**:471–481.
130. Young EA, Abelson JL, Cameron OG. Interaction of brain noradrenergic system and the hypothalamic-pituitary-adrenal (HPA) axis in man. *Psychoneuroendocrinology* 2005;**30**:807–814.
131. Savitz J, Lucki I, Drevets WC. 5-HT(1A) receptor function in major depressive disorder. *Prog Neurobiol* 2009;**88**:17–31.
132. Schmahl CG, McGlashan TH, Bremner JD. Neurobiological correlates of borderline personality disorder. *Psychopharmacol Bull* 2002;**36**:69–87.
133. Bremner JD. Does stress damage the brain? *Biol Psychiatry* 1999;**45**:797–805.
134. Rinne T, de Kloet ER, Wouters L, Goekoop JG, de Rijk RH, Van Den Brink W. Fluvoxamine reduces responsiveness of HPA axis in adult female BPD patients with a history of sustained childhood abuse. *Neuropsychopharmacology* 2003;**28**:126–132.
135. Laplante P, Diorio J, Meaney MJ. Serotonin regulates hippocampal glucocorticoid receptor expression via a 5-HT7 receptor. *Brain Res Dev Brain Res* 2002;**139**: 199–203.
136. Smythe JW, Rowe WB, Meaney MJ. Neonatal handling alters serotonin (5-HT) turnover and 5-HT2 receptor binding in selected brain regions: Relationship to the handling effect on glucocorticoid receptor expression. *Brain Res Dev Brain Res* 1994;**80**:183–189.
137. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Struct Funct* 2008;**213**:93–118.
138. Drevets WC. Neuroimaging studies of mood disorders. *Biol Psychiatry* 2000;**48**:813–829.
139. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: A meta-analysis. *Am J Psychiatry* 2004;**161**:598–607.
140. Bremner JD, Vythilingam M, Vermetten E, Vaccarino V, Charney DS. Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. *Am J Psychiatry* 2004;**161**:637–645.
141. Schmahl C, Bremner JD. Neuroimaging in borderline personality disorder. *J. Psychiatric Res.* 2006;**40**:419–427.
142. Yehuda R. Post-traumatic stress disorder. *N Engl J Med* 2002;**346**:108–114.
143. Sapolsky RM. Atrophy of the hippocampus in posttraumatic stress disorder: How and when? *Hippocampus* 2001;**11**:90–91.
144. Sapolsky RM. Chickens, eggs and hippocampal atrophy. *Nat Neurosci* 2002;**5**:1111–1113.
145. Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci* 2002;**22**:6810–6818.
146. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. *Nat Rev* 2009;**10**:423–433.
147. Yang TT, Hsiao FH, Wang KC, et al. The effect of psychotherapy added to pharmacotherapy on cortisol responses in outpatients with major depressive disorder. *J. Nervous Mental Disease* 2009;**197**:401–406.