EXPERT REVIEWS

Cognitive correlates of hypothalamic–pituitary–adrenal axis in major depression

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Depressive disorder has become a major health problem and is ranked among the leading causes of disability worldwide. Depression-related cognitive impairment contributes to loss of economic productivity and psychosocial functioning and calls for more efficient treatment strategies. Although the pathogenesis of cognitive impairments in patients with major depressive disorder (MDD) is still insufficiently understood, increasing evidence implicates hypothalamus–pituitary–adrenal (HPA) axis as an important neurobiological determinant of cognitive impairment in depression. In this article, major findings of both HPA axis function abnormalities and cognitive impairments in depressed patients are summarized, focusing on their inter-relationship. Novel approaches in pharmacotherapy and psychotherapy have emerged which will be discussed with regard to their ability to reinstate normal HPA axis function in MDD and to treat cognitive impairments in MDD.

Keywords: amygdala • cognition • cortisol • hippocampus • HPA axis • human • major depressive disorder • memory • pharmacotherapy • psychotherapy

Alterations in hypothalamic–pituitary–adrenal (HPA) axis function, such as hypercortisolism and reduced feedback sensitivity, have been a prominent finding in neuroendocrine investigations of major depressive disorder (MDD). Cognitive impairments, particularly those concerning attention, memory and executive function have also consistently been reported in MDD. However, the causes of these cognitive deficits remain unclear. Several studies have investigated the relationship between HPA axis dysfunction and neuropsychological impairment in MDD. After a brief introduction to HPA axis function, we will provide an overview of the evidence of HPA axis dysfunction on the one hand and cognitive impairment on the other hand in MDD. Following a summary of glucocorticoid (GC) action on cognitive function in healthy human participants, we will then present a review of the findings investigating relationships between HPA axis dysfunction and neuropsychological impairment in patients with MDD. Finally, we will selectively describe psychopharmacological and psychotherapeutic intervention studies addressing HPA axis regulation and associated cognitive function in MDD.

HPA axis function

In response to a physical or psychological stressor, the HPA system becomes activated, resulting in a 'cascade' of hormone release. Corticotropin-releasing hormone (CRH) and arginine vasopressine (AVP) are secreted from neurons in the paraventricular nucleus (PVN) of the hypothalamus which in turn stimulate the synthesis and release of adrenocorticotropic hormone (ACTH), also known as corticotropin, in the anterior pituitary. ACTH then promotes the release of GCs (mainly corticosterone in rodents, and cortisol in humans and primates) from the adrenal cortex. Cortisol exerts negative feedback on the hypothalamus and pituitary to inhibit the synthesis and secretion of CRH and ACTH, respectively, in order to maintain a homeostasis of circulating GCs. In addition, the hippocampus exerts negative feedback on the PVN, thereby reducing HPA axis activity.

Cortisol binds to two subtypes of intracellular corticosteroid receptors, the mineralocorticoid receptor (MR), also referred to as the type I receptor, and the GC receptor (GR) or type II receptor. Recently, membrane-bound GRs and MRs have also been identified [1,2]. GRs are widely distributed throughout the

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brain, with high densities in the prefrontal cortex (PFC), hippocampus, amygdala, thalamus and hypothalamus. MRs have been found mostly in the hippocampus, amygdala and PFC [3]. The two receptor types differ in their binding properties with (intracellular) MRs having a six- to tenfold higher affinity for cortisol [4]. Under basal conditions, MRs are thus substantially occupied, while it is only when under stress that the majority of GRs become occupied.

HPA axis alterations in MDD

In MDD, several abnormalities concerning HPA axis function under basal conditions or following provocation through endocrine or psychological challenge tests have been identified [5–8]. Concerning HPA axis function under basal conditions, a significant percentage of depressed patients show increased 24-h levels of cortisol, with an enhanced cortisol release after awakening [9,10] and an elevated trough level in the evening resulting in a flattened circadian rhythm (Figure 1) [11–13]. However, reduced diurnal cortisol levels have been found as well, mainly in atypical depression [14] and depression with comorbid anxiety disorder [12]. Furthermore, depressed patients show a blunted ACTH response to CRH administration [15,16], suggesting desensitized CRH receptors at the pituitary level, which may be a consequence of hypersecretion of central CRH [11]. Furthermore, depressed patients show higher cortisol levels than nondepressed individuals following exposure to psychological stressors [6]. One of the most consistent findings in MDD is a failure to suppress cortisol secretion in the dexamethasone suppression test (DST) in a large percentage of patients with depression, mainly with psychotic features [17]. As dexamethasone only binds to GRs, but not MRs, elevated cortisol levels after dexamethasone administration have been interpreted as an indicator of reduced GR sensitivity at the level of the pituitary in depression. To gain further insight into HPA feedback regulation, a more sensitive measure – the combined dexamethasone/CRH (DEX/CRH) test – was developed [11]. In this test, patients are pretreated with oral dexamethasone and given an infusion of CRH on the following day. In the DEX/CRH test, depressed patients exhibit enhanced secretion of ACTH and cortisol, which represents an impaired feedback of the HPA axis. Moreover, it was shown that an elevated cortisol response in either the DST or DEX/CRH test was associated with a higher risk for relapse [18–20] and a poorer treatment response [21]. In addition to reduced GR sensitivity, recent studies have also found altered MR receptor function in depressed patients [22]. Pariante and colleagues developed a challenge test using prednisolone, a synthetic GC, which is highly similar to natural cortisol and binds both to GRs and MRs [23]. Studies using this test observed that depressed patients show a normal suppression to prednisolone in contrast to nonsuppression after dexamethasone administration. This has been interpreted as preserved MR functioning [24]. Based on the findings of preserved or even enhanced MR sensitivity, it was speculated that (hyper) function of MRs might compensate for reduced GR function, leading to a normal feedback response in depressed patients when both GRs and MRs are probed [25]. With regard to neurobiological and neuroanatomical alterations, elevated concentrations of CRH in the cerebrospinal fluid [26] and decreased GR mRNA expression in the prefrontal cortex [27,28] have been found in patients with MDD. Moreover, an increased size of the pituitary [29] and adrenal glands [30] has been reported.

Taken together, the abnormal results in HPA axis function in MDD have been interpreted as reflecting an exaggerated CRH drive and/or a reduced functioning of GRs. A possible shift of the MR/GR balance seems to play an important role in the pathogenesis of depression [31,32]. In support of this notion are recent findings indicating that single nucleotide polymorphisms in the GR and MR genes are associated with an increased risk of MDD [33–35].

Cognitive impairments in MDD

Cognitive disturbances such as lack of concentration and indecisiveness are some of the core symptoms of MDD diagnosis according to the Diagnostic and Statistic Manual (DSM)-IV [36]. Beneath the clinical picture, a substantial amount of studies using neuropsychological assessment have shown that attention, declarative memory and executive function are impaired in MDD [37–39].

Depressed patients show disturbances of selective and divided attention as well as vigilance, and have found to be delayed in 'speeded tasks' [40]. In addition, an attentional bias toward negative stimuli has consistently been reported [41]. Regarding executive function, flexibility and semantic fluency are predominantly impaired in MDD [37,42]. Deficits in declarative memory have also been well documented. Gorwood and colleagues showed that memory performance was reduced by 2–3% with every prior depressive episode [43]. Studies investigating autobiographical memory have described the phenomenon of 'overgeneral autobiographical memory' in MDD patients as they are prone to recall events of their past in categories rather than retrieving a single episode [44]. On average, the reported cognitive impairments have been described as only moderate; however, 21% of patients with MDD show significant impairments in at least two neuropsychological domains compared with only 4% in healthy individuals [45]. Deficits in attention and executive function have been discussed as trait variables of MDD as those deficits seem to persist throughout clinical remission [46]. Neuropsychological impairment in MDD has partly been related to structural brain abnormalities; however, the heterogeneity of results makes it difficult to determine direct causal pathways. In MDD patients, volume reductions have been reported in the PFC, anterior cingulate cortex, basal ganglia and hippocampus [47,48]. Amygdala volume has been found to change dynamically throughout the course of illness, being enlarged in the first period and reduced with illness progression [48]. Regarding functional abnormalities, Drevets and colleagues postulate an attenuated function of medial prefrontal cortex (MPFC), which results in disinhibition of amygdala activity [47].

In conclusion, considerable evidence exists of both HPA axis dysfunction and cognitive disturbances in MDD, the relationship of which has just become a target of investigation.

HPA axis & cognitive function in healthy human subjects

In this section we discuss how the HPA axis influences cognitive functions in healthy human participants. For more detailed information, including work from animal studies, we refer the reader to exquisite reviews available on this topic (see [49–58]).

The majority of studies investigating the impact of GCs on cognition in healthy human participants have concentrated on memory function, particularly episodic and working memory. Episodic memory refers to information that is encoded in a particular context and is related to time and space [59]. Working memory can hold information in recent memory storage and perform mental operation on the retained information [60]. In addition, long-term memory can be divided into three different phases referred to as acquisition (the learning process), consolidation (memory storage) and retrieval (access to stored information). Neuroanatomically, episodic memory performance has been linked to the hippocampus, while working memory performance seems to be strongly related to the PFC. As already pointed out, both the hippocampus and PFC are characterized by a substantial amount of GRs.

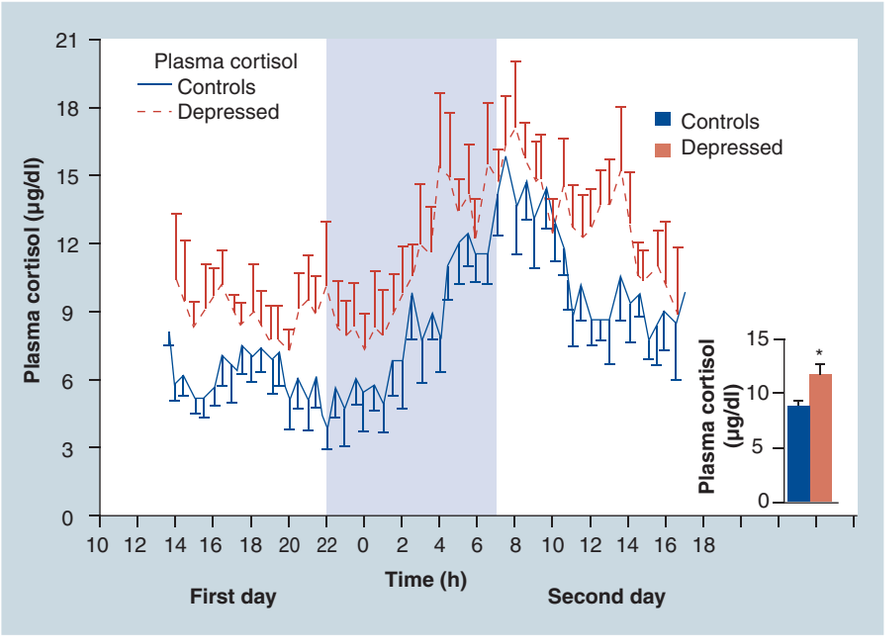

Figure 1. Diurnal curves of plasma cortisol levels (mean ± standard error) in 14 healthy volunteers and ten patients with major depression, melancholic type. The shaded area represents data recorded with the lights off (23:00–07:00 h). The bar graph inserted in the right corner represents the average of the mean value for the series of hormonal measurements (mean ± standard error).
*p < 0.02.
Taken from [13]. © 2000 National Academy of Sciences, USA.

The impact of GCs on episodic memory has been shown to depend on the different memory phases investigated. While memory retrieval processes are impaired through activation of GRs either after acute or chronic cortisol treatment [61–64], memory consolidation is usually enhanced [65–67]. However, results have been somewhat inconsistent [68,69]. The effects of GCs on working memory have received less attention. In some studies, acute cortisol administration has been found to impair working memory [70–72], while other studies failed to find impairing effects [73,74]. Only one study has investigated the effects of GCs on autobiographic memory retrieval in healthy subjects. It was shown that memories of past personal events were significantly less specific after acute administration of hydrocortisone compared with placebo treatment [75].

The acute impact of cortisol has been found to be typically greater for emotionally arousing stimuli than for neutral stimuli [73,74]. In this context, Roozendaal and colleagues have demonstrated that noradrenergic activation in the basolateral amygdala (BLA) is essential for the modulating effects of GCs on different memory functions and related brain structures (e.g., the hippocampus) [76].

The relationship between cortisol and cognition appears to follow an inverted U-shaped dose–response curve with extremely high and low levels of cortisol impairing memory, and intermediate levels enhancing memory consolidation [49,50,53]. The effect of the neurobiological substrate of GC on memory is becoming increasingly understood. An important aspect that has been focused on in this context is hippocampal long-term potentiation (LTP), a phenomenon which refers to strengthening of synaptic contacts by repeated stimulation and which is known to be involved in memory storage. Plasma cortisol levels have found to be negatively correlated with hippocampal LTP [77]. Consistent with the proposed inverted U-shaped dose–response curve of GC effects, basal levels of GCs are essential for effective LTP, while higher levels impair it [48]. Moreover, functional imaging studies revealed a reduced activation of different brain structures associated with memory performance (e.g., the medial temporal lobe, hippocampus and superior frontal gyrus) after cortisone treatment [78,79].

It is increasingly recognized that prolonged activation of the immune system and its associated release of cytokines can negatively influence brain functions involved in the regulation of affective and cognitive processes [80]. In parallel, the HPA axis is activated. It is tempting to speculate that some of the associations between cortisol and cognition are mediated by inflammatory processes [80].

In summary, GC effects on declarative memory depend on the memory phase tested and are hypothesized to follow an inverted U-shaped dose–response curve. Several research groups have replicated that cortisol impairs delayed memory retrieval and enhances memory consolidation, particularly for emotionally arousing material. The latter observation supports the close interaction between the sympathetic nervous system and the HPA axis, which is shown, for example, by the results from animal

studies that GC can only exert effects on memory in the presence of adrenergic activity in the amygdala [76]. Detrimental effects of GCs on working memory have also been found in some studies. A dynamic interaction between the BLA and other brain regions (e.g., hippocampus, PFC) has been assumed to modulate the opposing effects of GCs on memory consolidation and memory retrieval [76]. In addition, GC-induced inhibition of LTP, reduced activation of memory-related brain structures and interaction of the HPA axis with the immune system might be involved.

HPA axis & cognitive function in MDD

The reported structural and functional brain abnormalities in patients with MDD have been related partly to the dysregulation of the HPA axis. Chronic stress causes retraction of dendrites referred to as 'dendritic atrophy' in the CA3 region of the hippocampus [81]. Thus, volume reduction of the hippocampus in MDD could either result from chronic hypercortisolemia or early life stress and its long-lasting impact on this structure. This is supported by results of an association of early trauma [82] and duration of depressive illness [83,84] with hippocampal volume. However, besides a direct impact of GCs on hippocampal neurons, the reported effects might be mediated through a GC-induced dysregulation of neurotransmitter systems (e.g., catecholamines). In addition to GCs causing hippocampal dendritic atrophy, a reduced hippocampal volume might reversely contribute to hypercortisolemia in terms of a 'vicious cycle', as the hippocampus represents one of the main brain structures providing inhibitory feedback control over the HPA axis. Recent studies indicate that hippocampal atrophy following stress exposure is reversible due to dendritic remodeling or neurogenesis across the lifespan [85]. However, the process of neurogenesis is impaired in animal models of depression. Since GCs have been shown to suppress neurogenesis, it is tempting to speculate that they might be involved in the reduced neurogenesis thought to occur in depression [86].

Besides the hippocampus, limbic structures are also involved in the regulation of circulating GCs. The amygdala mediates the stress response through disinhibition of CRH release from the hypothalamic PVN. Thus, Drevets and colleagues conclude from their model that a dysfunctional MPFC together with amygdala hyperactivity might not only account for the neuropsychological deficits but also for the HPA axis hyperactivity in MDD [47].

Investigations of a possible relationship between HPA axis dysregulation and cognitive impairments in patients with MDD were first initiated by findings in patients with Cushing's disease (CD). Similar to a significant proportion of patients with MDD, patients with CD are characterized by chronically elevated cortisol levels, though the etiology in the latter group differs (e.g., tumors of the pituitary/adrenal glands or excessive administration of exogenous GCs) and hypercortisolism is more pronounced. Patients with CD often suffer from depressive symptoms [87] and are impaired in cognitive function [88]. Based on those obvious similarities it was speculated that hypercortisolemia might play an important role in the etiology of depression and associated cognitive disturbances.

Studies investigating the relationship between cognitive impairment and HPA axis dysfunction in patients with MDD can be separated into two approaches. Most studies have addressed the relationship by correlating measures of HPA axis function, either basal function or feedback sensitivity through administrating challenge tests (DST, DEX/CRH-test or the prednisolone test), with neuropsychological performance. However, at least two studies have used experimental designs to investigate GC effects on cognition by manipulating HPA axis function through acute cortisone treatment in patients with MDD [89,90].

Correlational studies of basal HPA axis measures & cognitive function in MDD

There are several studies that correlated baseline measures of cortisol, either in salivary, blood or urine, with neuropsychological performance of patients with MDD (Table 1). In one of the first studies, Rubinow and colleagues reported a negative correlation between mean urinary free cortisol (UFC) levels in depressed patients and the number of errors made on the Halstead category test, a measure of abstract thinking [91]. This is in line with the finding of a significant correlation between visual memory impairment and cortisol levels in MDD patients observed in another study [92]. Accordingly, in a study by Sikes and associates, neuropsychological performance in 60 patients with MDD was negatively correlated with UFC, but not plasma cortisol [93]. In patients with recurrent major depression, Egeland and colleagues found that high levels of morning cortisol correlated with executive dysfunction and impaired verbal memory storage and retrieval but not with information processing speed. Depression severity was not associated with cortisol level but related to impaired information processing [94]. Furthermore, plasma cortisol levels were negatively correlated with verbal declarative memory, psychomotor speed and executive function in another study with a psychotic subgroup [95]. Moreover, it has been demonstrated that in patients with MDD, plasma cortisol concentrations were negatively correlated with general intellectual function; however, no relationship with verbal declarative memory could be detected in this study [96].

Indeed, not all studies could confirm an association between cortisol and cognitive performance. A lack of an association between cortisol and cognitive function was reported by Michopoulos and colleagues [97]. They found cortisol level and either visuospatial memory or executive function showed no correlation in female MDD patients with melancholic features. Concurrent with these results, in a sample of MDD patients with psychotic features, no correlation of plasma cortisol with verbal declarative memory was found [98]. Only one correlational study investigated autobiographical memory performance and HPA axis function in patients with MDD and revealed that baseline cortisol levels were not related to autobiographical memory performance [99].

In a study by den Hartog and associates, a significant negative association between a flatter baseline curve (Δ cortisol) of salivary cortisol and cognitive speed was found [100]. This association disappeared, however, after controlling for depressive symptoms,

which is in line with another study reporting an association between cortisol and cognitive performance in depressed patients as well as healthy controls [95]. Gomez and colleagues also found a negative association between plasma cortisol level and verbal declarative memory in depressed patients and healthy control subjects. However, a negative correlation between cortisol and executive function was revealed only in the healthy subjects [101]. Thus, this study suggests that a negative association between cortisol levels and cognition seems to be a general finding and not specific to depression.

A limitation to most of the studies reviewed in this article is that patients were either medicated or that no healthy control group was included. These two major methodological requirements were met by the group of Hinkelmann and colleagues, who demonstrated that morning cortisol was related to impairments in verbal declarative memory, visuospatial memory and executive function in an unmedicated sample of 52 patients with MDD, but not in the control group [102].

In summary, most but not all studies suggest an association between basal cortisol levels and cognitive performance, which might be more relevant in patients with MDD due to higher cortisol levels compared with healthy controls. It has been questioned whether these findings are due to the depressive episode *per se* or whether they reflect a pre-existing risk factor. Interestingly, a recent study found a stronger negative correlation between verbal declarative memory and cortisol secretion in high-risk healthy women who had a depressed parent compared with healthy women without a family history of depression [103], but the correlations did not differ significantly from each other. It must be mentioned that in this context there is evidence for HPA axis dysfunction in healthy subjects with high familial risk for depression [104,105].

In addition to neuropsychological function, a study by Vythilingam and associates also assessed hippocampal volume in 38 outpatients with MDD [106]. In contrast to the significant correlations indicated by the former studies, the authors reported that baseline plasma or UFC was not associated with either hippocampal volume or neuropsychological performance. However, no difference in hippocampal volume between depressed patients and controls was revealed. Future studies should further investigate the association between structural brain changes, HPA axis dysfunction and cognition.

As mentioned previously, correlational analyses between basal cortisol release and cognition yielded mixed results, thus, the use of more sensitive measurement of HPA axis function might be helpful. A subset of studies have used the DST, the more sensitive DEX/CRH test or prednisolone test to target the relationship between HPA axis feedback dysfunction and cognitive impairment in MDD (Table 1). In one of the first studies using the DST, it was shown that depressed cortisol nonsuppressors had a longer reaction time in a key pressing task compared with depressed cortisol suppressors [107]. Moreover, a negative association between cortisol nonsuppression in the DST and memory performance assessed by mental status examination has been reported in 327 depressive inpatients [108]. Sikes and colleagues reported a significant negative association between cortisol nonsuppression in the DST and neuropsychological performance [93]. Conversely, Caine *et al.* demonstrated that cortisol nonsuppression did not correlate with either performance in verbal declarative memory, visual memory or executive function in 20 depressed inpatients [109]. Accordingly, DST nonsuppression was not associated with visual memory performance in the study by Wauthy and colleagues [92]. This was also confirmed by Wolkowitz *et al.* who found no significant difference in verbal recognition performance between depressed cortisol suppressors, depressed nonsuppressors and healthy control subjects, although depressed nonsuppressors showed a higher rate of errors of commission ('false alarms') [110].

In a longitudinal study, it was demonstrated in 64 patients with unipolar MDD, that a post-treatment normalization of HPA activity reflected by a decreased cortisol response in the DEX/CRH test after treatment with the SSRI citalopram was correlated with an improvement in working memory, but not with improvements in verbal declarative memory, sustained attention or global severity of depressive symptoms [111]. This is consistent with the results of studies in healthy human subjects where working memory was found to be more sensitive to GCs than verbal declarative memory [70]. By contrast, in a second longitudinal study by Reppermund and colleagues, a decreased cortisol response in the DEX/CRH test and improvement in working memory was not associated, either in remitted or nonremitted patients prior to discharge from hospital [112]. However, verbal short-term memory was significantly correlated with reduced cortisol responses in the DEX/CRH prior to discharge from hospital in nonremitted patients. Severity in depression was not related to cortisol responses but negatively correlated with selective attention and speed of information processing. In a prospective study using the recently introduced prednisolone test, cognitive performance assessed through Mini-Mental State Examination was not correlated with either basal cortisol level or post-prednisolone cortisol response at admission and discharge from hospital in depressed inpatients classified as moderately treatment resistant to antidepressant therapy [113]. Thus, the relationship between HPA axis feedback sensitivity and cognition needs further investigation. In these studies, sensitive neuropsychological measures should be employed.

In summary, there is some support for the hypothesis that neuropsychological impairment observed in depression is associated with the concomitant hypercortisolemia or impaired negative feedback in HPA axis function, as 14 out of 20 studies indicated significant correlations between cortisol level and cognitive impairment in patients with MDD. One methodological issue explaining, at least in part, the rather large variance of the data is related to the issue of the rather low reliability of some of the basal cortisol measurements employed. Furthermore, some of the neuropsychological measurements were either rather broad (e.g., Mini-Mental State Examination) or rather narrow (e.g., just a single test). Future studies should employ cognitive test batteries containing several sensitive cognitive measures.

In addition, results of cross-sectional studies have to be interpreted with caution as they do not allow causal conclusions. Especially the relationship between GR functioning and cognition

Table 1. Correlational studies of cognitive impairments and hypothalamus–pituitary–adrenal axis dysfunction in major depressive disorder (cont.).

Study (year)	MDD patient characteristics	Sample size (MDD vs controls)	HPA assessment	Neuropsychological assessment	Main results	Ref.
Brown and Qualls (1981)	Inpatients; medicated; mean age: 42 years (SD: NR; range: 24–61)	39 vs no controls	DST	Reaction time	DST nonsuppressors (n = 18) had a significantly longer reaction time than DST suppressors	[107]
Caine *et al.* (1984)	Inpatients; drug-free; melancholic; mean age: 40 years (SD: 15; range: NR)	20 vs no controls (13 melancholic)	DST	Verbal declarative memory; visual memory; executive function	Ten patients nonsuppressors in DST; DST-nonsuppression not correlated with neuropsychological performance	[109]
Rubinow *et al.* (1984)	Inpatients; drug-free; bipolar; mean age: 40 years (SD: 3; range: 20–69); age of MDD patients was greater than controls	28 vs 31 (eight unipolar; 12 bipolar I; eight bipolar II)	UFC	Abstracting ability	Cortisol level negatively correlated with abstracting ability in depressed patients, mediated by age; symptom severity not correlated with abstracting ability	[91]
Winokur *et al.* (1987)	Inpatients; medication NR; bipolar; melancholic; atypical; schizoaffective; cyclothymia; dysthymia; mean age and age range NR	327 vs no controls	DST	Memory	164 patients nonsuppression in DST; nonsuppression negatively correlated with memory performance	[108]
Sikes *et al.* (1989)	No characteristics reported	60 vs no controls	DST; baseline plasma cortisol and UFC	Neuropsychological test battery (e.g., rey, category test or pegboard)	23 patients nonsuppression in DST; nonsuppression and UFC negatively correlated with cognitive performance; plasma cortisol not correlated with cognitive performance	[93]
Wolkowitz *et al.* (1990)	Drug-free; mean age and age range NR	21 vs 12	DST; baseline serum cortisol	Verbal declarative memory (recognition)	Nine patients nonsuppressors in DST; no significant difference between depressed cortisol suppressors, nonsuppressors and control subjects on total score; depressed nonsuppressors showed higher rate of errors of commission; depressed patients' baseline cortisol levels tended to correlate with numbers of commission errors	[110]
Wauthy *et al.* (1991)	Inpatients; medication NR; bipolar; melancholic; nonpsychotic; mean age: 46 years (SD: 11; range: NR)	16 vs no controls (three bipolar)	DST	Visual memory	Six patients nonsuppressors in DST; DST-nonsuppression not correlated with visual memory; cortisol level negatively correlated with visual memory	[92]
Van Londen *et al.* (1998)	In- and outpatients; drug-free; bipolar; psychotic; melancholic; mean age: 47 years (SD: 15; range: 22–77)	49 vs no controls (eight bipolar; five psychotic; 27 melancholic)	Baseline plasma cortisol	Verbal declarative memory; general intellectual function	Cortisol level negatively correlated with general intellectual function; no correlation with verbal declarative memory; symptom severity negatively correlated with neuropsychological performance	[96]

DEX/CRH test: Combined dexamethasone/corticotropin releasing hormone test; DST: Dexamethasone suppression test; HAMD: Hamilton Depression Rating Scale; HPA: Hypothalamus–pituitary–adrenal; MDD: Major depressive disorder; MMSE: Mini-Mental State Examination; NR: Not reported; SD: Standard deviation; SSRI: Selective serotonin-reuptake inhibitor; UFC: Urinary free cortisol.

Table 1. Correlational studies of cognitive impairments and hypothalamus–pituitary–adrenal axis dysfunction in major depressive disorder (cont.).

Study (year)	MDD patient characteristics	Sample size (MDD vs controls)	HPA assessment	Neuropsychological assessment	Main results	Ref.
Belanoff *et al.* (2001)	Psychotic and nonpsychotic; drug-free; mean age: 47 years (SD: 16; range: 24–75)	27 vs ten (ten psychotic; 17 nonpsychotic)	Baseline plasma cortisol	Verbal declarative memory	Elevated cortisol and flatter basal cortisol curve in psychotic patients; cortisol level not correlated with verbal declarative memory; verbal declarative memory impaired in psychotic patients, symptom severity not correlated with verbal declarative memory	[98]
den Hartog *et al.* (2003)	Outpatients; drug free; nonpsychotic; mean age: 42 years (SD: 13; range: NR)	27 vs 36 (+20 patients with allergic rhinitis)	Baseline salivary cortisol	Verbal declarative memory; cognitive speed	Elevated evening cortisol level and flatter basal (Δ) cortisol curve in MDD patients vs controls; Δ cortisol (flatter curve) negatively correlated with cognitive speed, influenced by depressive symptoms	[100]
Vythilingam *et al.* (2004)	Outpatients; 7 months treatment with fluoxetine/ sertraline (SSRI); no history of trauma; mean age: 41 years (SD: 11; range: NR); age of MDD patients was greater than controls	38 vs 33	DST; baseline plasma cortisol and UFC	Verbal and visual declarative memory; attention; psychomotor speed; executive function; hippocampal volume	No difference in baseline cortisol level and DST between patients and controls; cortisol level not correlated with neuropsychological performance and hippocampal volume; no difference in hippocampal volume in patients vs controls; verbal declarative memory impaired in patients	[106]
Zobel *et al.* (2004)	Inpatients; recurrent episodes; nonpsychotic; 4 weeks treatment with citalopram (SSRI); mean age: 47 years (SD: 15; range: 19–65)	64 vs no controls	DEX/CRH test	Verbal declarative memory; working memory; sustained attention	Decrease in DEX/CRH response after SSRI treatment positively correlated with working memory; DEX/CRH response not correlated with reduction in symptom severity	[111]
Barnhofer *et al.* (2005)	In- and outpatients; medicated; mean age: 30 years (SD: 8; range: NR)	47 vs no controls	Baseline salivary cortisol	Autobiographical memory	Cortisol level not correlated with autobiographical memory; cortisol decrease negatively correlated with autobiographical memory; cortisol level not correlated with symptom severity	[99]
Egeland *et al.* (2005)	In- and outpatients; recurrent episodes; medicated; mean age: 36 years (SD: 9; range: 20–50)	26 vs no controls	Morning salivary cortisol	Verbal declarative memory; executive function; psychomotor speed	Cortisol level negatively correlated with verbal declarative memory and executive function; no correlation between cortisol level and symptom severity; symptom severity negatively correlated with psychomotor speed	[94]

DEX/CRH test: Combined dexamethasone/corticotropin releasing hormone test; DST: Dexamethasone suppression test; HAMD: Hamilton Depression Rating Scale; HPA: Hypothalamus–pituitary–adrenal; MDD: Major depressive disorder; MMSE: Mini-Mental State Examination; NR: Not reported; SD: Standard deviation; SSRI: Selective serotonin-reuptake inhibitor; UFC: Urinary free cortisol.

Table 1. Correlational studies of cognitive impairments and hypothalamus–pituitary–adrenal axis dysfunction in major depressive disorder (cont.).

Study (year)	MDD patient characteristics	Sample size (MDD vs controls)	HPA assessment	Neuropsychological assessment	Main results	Ref.
Gomez *et al.* (2006)	In- and outpatients; medicated; psychotic and nonpsychotic; melancholic; mean age: 38 years (SD: 13; range: NR)	53 vs 26 (29 psychotic, 24 nonpsychotic)	Baseline plasma cortisol	Verbal declarative memory; attention; psychomotor speed; working memory; semantic fluency; executive function	Elevated cortisol level in psychotic patients vs nonpsychotic patients and controls; cortisol level negatively correlated with verbal memory and psychomotor speed and executive function in patients and controls	[95]
Reppermund *et al.* (2007)	Inpatients; (remitted/ nonremitted at discharge); medicated; mean age: 45 years (SD: 10; range: 21–62)	75 vs no controls (51 remitted, 24 nonremitted)	DEX/CRH test	Verbal short-term memory; selective attention; divided attention; verbal working memory; speed of information processing	No decrease in DEX/CRH cortisol response at discharge in nonremitters vs remitters; DEX/CRH cortisol response not correlated with neuropsychological performance in remitted patients; DEX/CRH response negatively correlated with short-term memory in nonremitted patients at discharge; symptom severity (HAMD) negatively correlated with selective attention and speed of information processing; no correlation of symptom severity with DEX/CRH cortisol response	[112]
Michopoulos *et al.* (2008)	Inpatients; only female; medicated; melancholic and nonmelancholic; mean age: 53 years (SD: 11; range: NR)	40 vs 20 (20 melancholic; 20 nonmelancholic)	Baseline plasma and salivary cortisol	Visuospatial memory; executive function	No difference in cortisol levels of melancholic vs nonmelancholic patients and patients vs controls; cortisol level not correlated with neuropsychological function; no correlation of symptom severity with cortisol level	[97]
Gomez *et al.* (2009)	Outpatients; drug-free; nonpsychotic; melancholic; mean age: 41 years (SD: 13; range: NR)	37 vs 18	Baseline plasma cortisol	Verbal declarative memory; executive function	No group difference in cortisol level; cortisol level negatively correlated with verbal declarative memory in patients and controls and with executive function in controls only	[101]
Hinkelmann *et al.* (2009)	In- and outpatients; drug-free; nonpsychotic; mean age: 35 (SD: 11; range: NR)	52 vs 50	Baseline salivary cortisol	Verbal declarative memory; visuospatial memory; working memory; selective attention; executive function	Elevated morning cortisol level in patients vs controls; cortisol level negatively correlated with verbal declarative memory, visuospatial memory, executive function in depressed patients	[102]

DEX/CRH test: Combined dexamethasone/corticotropin releasing hormone test; DST: Dexamethasone suppression test; HAMD: Hamilton Depression Rating Scale; HPA: Hypothalamus–pituitary–adrenal; MDD: Major depressive disorder; MMSE: Mini-Mental State Examination; NR: Not reported; SD: Standard deviation; SSRI: Selective serotonin-reuptake inhibitor; UFC: Urinary free cortisol.

Table 1. Correlational studies of cognitive impairments and hypothalamus–pituitary–adrenal axis dysfunction in major depressive disorder (cont.).

Study (year)	MDD patient characteristics	Sample size (MDD vs controls)	HPA assessment	Neuropsychological assessment	Main results	Ref.
Juruena *et al.* (2009)	Inpatients; medicated; moderately treatment resistant to antidepressants; mean age: 51 (SD: 1.5; range: NR)	45 vs 46	Prednisolone test; baseline salivary cortisol	MMSE	Elevated baseline cortisol level in patients vs controls; elevated cortisol level after prednisolone administration in patients vs controls; no significant difference in cortisol suppression between patients and controls after prednisolone administration; baseline cortisol level and prednisolone cortisol response not correlated to MMSE performance	[113]

DEX/CRH test: Combined dexamethasone/corticotropin releasing hormone test; DST: Dexamethasone suppression test; HAMD: Hamilton Depression Rating Scale; HPA: Hypothalamus–pituitary–adrenal; MDD: Major depressive disorder; MMSE: Mini-Mental State Examination; NR: Not reported; SD: Standard deviation; SSRI: Selective serotonin-reuptake inhibitor; UFC: Urinary free cortisol.

has been investigated only rudimentally. Dexamethasone, which has been used in all but one of the correlational challenge studies, does not pass the blood–brain barrier and, therefore, the DST measures HPA axis feedback sensitivity only at the pituitary level [17]. As mentioned earlier, dexamethasone differs from cortisol with regards to its pharmacodynamic and pharmacokinetic properties and that it probes the function of GRs only. Thus, in addition to the reported correlational studies, investigations are needed, that use an experimental study design in MDD which will allow a comparison with the studies conducted in healthy subjects.

Experimental studies investigating the impact of GCs on cognition in MDD

To our knowledge, until recently only two studies investigated the association between HPA dysfunction and cognitive impairment by administrating synthetic cortisol to MDD patients prior to neuropsychological assessment. Bremner and colleagues found that verbal declarative memory was improved after 2-day treatment with dexamethasone (1 mg at 11 pm on the first day, 2 mg at 11 pm on the second day) in patients with MDD. In contrast, post-treatment memory function in healthy control subjects was reduced [89]. The authors concluded that a loss or hyposensitivity of GRs in the hippocampus could have resulted in a diminished negative effect of GCs on memory function in depressed patients. Further they argued that the apparent pattern of improvement in memory with dexamethasone in depression might be due to a reduction in cortisol after dexamethasone treatment.

In a recently published study by our working group, we investigated the effect of acute cortisol administration (10 mg of hydrocortisone) on autobiographical memory and found memory in healthy subjects to be impaired after cortisol treatment [90]. In patients with MDD, however, autobiographical memory performance was not affected after cortisol compared with placebo treatment (Figure 2). In the placebo condition, MDD patients performed generally worse than healthy control subjects, which is in line with previous reports [44]. We hypothesized that the lack of an effect of acute cortisol administration on memory performance might result from reduced sensitivity of hippocampal and/or prefrontal GRs.

The contradictory results of improved verbal declarative memory after dexamethasone treatment on the one hand [89] and unaffected autobiographical memory on the other hand [90] might be due to methodological differences, such as the usage of different GCs and different treatment designs (single acute vs sub-chronic prolonged).

Overall, studies on the association between HPA axis dysfunction and cognitive impairment in MDD have yielded controversial results. These might be at least partly explained by methodological differences concerning sample characteristics (i.e., subtype and severity of depression, gender, age, trauma history, medication, hospitalization status, and lack of control groups), HPA assessment, selection of neuropsychological instruments and time of testing (i.e., morning vs afternoon). Currently, the complexity of the results makes it difficult to postulate a causal relationship between HPA axis dysfunction and cognitive impairment in

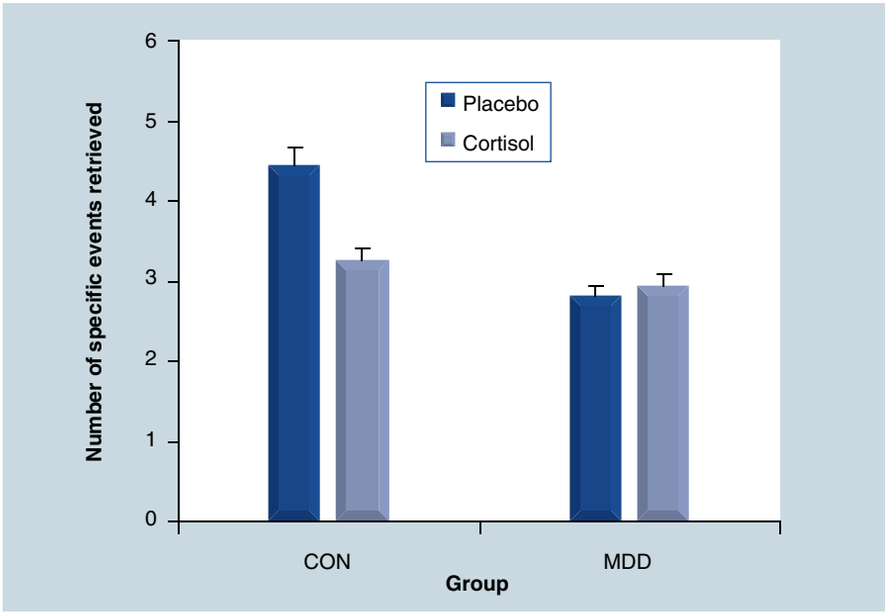

Figure 2. Mean number of specific memories in the autobiographical memory test in patients with major depressive disorder (n = 16) and healthy control subjects (n = 16) after placebo and hydrocortisone treatment. The autobiographical memory test assesses an individual's capacity to retrieve specific autobiographical life events. The number of specific events retrieved was significantly reduced after hydrocortisone compared with placebo treatment in healthy controls, but not in patients with MDD. These results are the first to provide experimental evidence for a reduced central glucocorticoid sensitivity in patients with MDD.
CON: Control; MDD: Major depressive disorder.
Taken from [90]; printed with permission from Elsevier.

MDD. As opposed to a causal relationship, it has been hypothesized that both HPA dysregulation and cognitive impairment might be 'downstream results of a central disturbance' [93]. Further studies with well-selected samples, experimental designs and sensitive measurements of HPA axis function are needed to elaborate appropriate models reconciling the diversity of findings.

Interventions targeting HPA axis dysfunction in MDD

The onset of a depressive episode is known to be associated with exposure to adverse early environments [114] and recent life stress [115,116]. A reduced ability to cope with stressful stimuli in patients with MDD seems to play an important role. The reported findings make it obvious that a maladaptive stress response in MDD patients might not only result from limited behavioral abilities to cope with stress, but also from neurobiological alterations of the stress response system, such as HPA axis dysfunction, at least in a subset of MDD patients. From a therapeutic viewpoint, it has been proposed that normalizing of HPA axis function would result in a reduction of depressive symptoms, as has been found in patients with CD [117]. A plethora of pharmacological studies investigated new antidepressant agents selectively targeting HPA axis function in patients with MDD. However, only recently, a second approach has emerged, with a small number of studies examining the effects of psychosocial interventions on HPA axis function in healthy human participants and patients with MDD.

Approaches in pharmacotherapy

The corticosteroid receptor hypothesis of depression has stimulated pharmacological research to strive for new antidepressant agents that act directly on different sites within the HPA axis [11]. These recently developed antiglucocorticoid agents consist of CRH1 receptor antagonists (e.g., R121919, Antarlamin), Vasopressin V1b receptor antagonists (e.g., SSR149415), cortisol synthesis inhibitors (e.g., metyrapone, ketoconazole), dehydroepiandrosterone (DHEA) and GR antagonists (e.g., mifepristone, Org 34517) (for recent reviews see [118–122]). However, despite initial promising results for mifepristone, the clinical utility of these new agents has not yet convincingly been demonstrated, as controlled trials in patients with MDD are lacking. A recent Cochrane meta-analysis indicated that anti-GCs serve as potential antidepressants, but only in nonpsychotic MDD patients [123].

To date, only one study has investigated the impact of anti-GCs on cognitive function in mood disorder [124]. In a double-blind cross-over study, 20 bipolar patients were treated with 600 mg/day of mifepristone or placebo for 1 week. In contrast to placebo treatment, spatial working memory, verbal fluency and spatial recognition memory significantly improved with mifepristone, irrespective of improvement in depressive symptoms. The improvement in cognition inversely correlated with basal cortisol levels. One may suggest that initially impaired GR function restored by the drug and a subsequently appropriate MR/GR balance could have accounted for the enhancement in cognitive performance.

Beyond the aforementioned new developments in pharmacotherapy of MDD, it has been assumed that the therapeutic effects of conventional monoaminergic antidepressant agents (e.g., monoaminoxidase inhibitors, and serotonin- or norepinephrine-reuptake inhibitors) can at least partly be ascribed to their attenuating impact on the HPA system (for reviews see [125,126]). This view is supported by the finding in animal studies that antidepressant drugs increase the binding capacity and expression of GC receptors in the hippocampus and other brain areas, with a subsequent decrease in CRH gene expression in the hypothalamic PVN and a downregulation of HPA axis activity [127–131]. *In vitro* experiments revealed that antidepressants increase the access of GCs to the brain through inhibition of membrane steroid transporters such as p-glycoprotein (PGP) at the blood–brain barrier [132]. This leads to a compensatory increased activation of GRs and MRs, thereby restoring HPA axis feedback function. An interaction between antidepressants and GCs also becomes apparent through the finding that

antidepressant action can be hastened by manipulating GR/MR function. A recent double-blind, randomized and placebo-controlled trial by Otte and colleagues in 64 in- and outpatients with MDD indicated that the stimulation of MR with fludrocortisone (an MR agonist) as adjunct treatment to escitalopram accelerated the treatment response in the group of responders while treatment with spironolactone (an MR antagonist) did not [133]. However, in a group of euthymic bipolar patients with residual symptoms, spironolactone as adjunctive treatment was effective in reducing symptoms [134]. Besides direct antidepressant action on GR function, a second, more indirect pathway via the serotonergic system through enhancement of postsynaptic serotonin type 1A (5-HT1A) receptor function was hypothesized [6]. Interestingly, the tricyclics imipramine and desipramine were shown to prevent downregulation of 5-HT1A receptors possibly mediated by simultaneously decreasing corticosterone levels and restoring an abnormal MR:GR ratio in chronically stressed rats, whereas the SSRIs zimelidine and fluoxetine did not affect corticosterone level or GR/MR balance and could not fully prevent downregulation of 5-HT1A mRNA [135]. The authors suggest that tricyclics are more effective because of their broader biochemical action affecting GC-associated neurotransmitter systems (e.g., cholinergic, noradrenergic and serotonergic). This implicates, that in SSRI or serotonin–norepinephrine reuptake inhibitors treatment-resistant depression, tricyclics might be a potential alternative.

A recent meta-analysis including 34 studies indicated that approximately 56% of depressed participants had similar cortisol levels before and after antidepressant treatment regardless of symptom improvement [136]. The largest mean effect sizes for the magnitude of change in cortisol levels from pre- to post-treatment were found for MDD patients with melancholic features. There is also evidence that MDD patients with comorbid anxiety disorder need special pharmacologic treatment, as it was assumed that comorbid patients might be characterized by both increased noradrenergic and CRH systems and, therefore, might show enhanced HPA axis activity compared with MDD patients without comorbidity [137]. However, data on HPA axis function in comorbid MDD patients are inconclusive and there is a need for further investigation. With regard to chronic depression, Watson and colleagues could not find abnormalities in HPA axis function, as neither the cortisol response to the DST or the DEX/CRH test differed significantly between patients and control subjects. This calls for further investigation of HPA axis function in this subgroup of patients [138].

In reversing the effects of stress on the hippocampus, antidepressants have also been demonstrated to increase neurogenesis as well as arborization and expression of brain-derived neurotrophic factor (BDNF) in hippocampal neurons [118], which represent possible key factors in enhancing cognitive performance.

To our knowledge, only two studies, which we have already mentioned [106,111], have investigated HPA axis function as well as cognitive performance following antidepressant treatment in MDD patients. In the study by Vythilingam and colleagues, a 7 months antidepressant treatment with the SSRIs fluoxetine and sertraline did result in a significant improvement in memory function and a reduction in UFC excretion, but did not alter hippocampal volume [106]. The authors concluded that antidepressants may improve hippocampal-mediated memory function without inducing structural changes. Zobel and associates found changes of the cortisol response to the DEX/CRH test after a 4-week treatment with the SSRI citalopram to be correlated with improvement of working memory [111].

In conclusion, both conventional antidepressants and new GC agents such as mifepristone might be potential candidates in treating cognitive dysfunction in patients with mood disorders. For anti-GC-induced changes in cognitive performance, an involvement of HPA axis alterations seems likely, and the same may be the case, at least in part, for conventional antidepressants. However, the available data are too sparse to draw final conclusions. Further studies are warranted investigating measures of both HPA and cognitive function following antidepressant and anti-GC treatment in patients with MDD.

Approaches in psychotherapy

A compelling finding underlining the importance of psychotherapeutic interventions for patients with MDD was reported by Nemeroff and colleagues. They demonstrated that in chronically depressed patients with a history of childhood trauma, psychotherapy alone was superior to antidepressant monotherapy [139]. Moreover, it has been reported that a history of childhood trauma increases HPA axis activity in depressed patients [140,141]. These results imply that not all depressed patients with HPA axis alterations will profit from new antidepressant agents and that it would be important to investigate if HPA axis dysfunction might also be affected by psychotherapy. Another important aspect constitutes the association of recent life stress and increased cortisol concentrations. In a sample of healthy adults in a naturalistic setting, Adam and colleagues found that on the one hand, some of the day-to-day variability in cortisol level reflect systematic changes in response to changing daily social and emotional experiences and, on the other hand, some daily subjective experiences (e.g., fatigue and physical complaints) appear to be influenced by day-to-day variations in cortisol levels [142]. Interestingly, an association between severe recent life stress and increased evening cortisol concentration has been reported for patients with MDD, but not for healthy control participants [12], possibly reflecting an impaired variability in cortisol response to psychosocial stressors in MDD. According to Adam and colleagues, it would not be effective to alter cortisol level pharmacologically, since a continuous responsivity of the cortisol system is important for responding to daily demands [143]. Alternatively, the authors propose providing the individual 'with the social and cognitive resources to better contain their affective responses to daily events', thereby enabling the individual to fine-tune their cortisol responses. A promising role for psychological interventions is further supported by a longitudinal study that examined post-treatment stress reactivity in MDD outpatients either treated with psychotherapy or medication [144]. The results

indicated that vulnerability to stressful events and an associated elevation of depressive symptoms occurred only in patients treated with medication. The authors concluded that psychotherapy provides patients with enhanced adaptive capacities and improved resilience to stress. The aforementioned assumptions are challenged by Thase and colleagues who reported a significant inverse relationship between 24-h UFC excretion and response to cognitive behavior therapy assessed by changes in Hamilton depression scale ratings in unmedicated depressed inpatients [145]. The authors hypothesized that this relationship is mediated by the negative impact of hypercortisolism on neurocognitve function, impairing patients' ability to recall, integrate and apply the methods in cognitive behavior therapy. In line with this, it has recently been demonstrated that stress prompts habit behavior at the expense of goal-directed behavior in healthy human participants [146], an interesting aspect that could have contributed to the low response rate to cognitive behavior therapy in MDD patients with hypercortisolemia. However, in the study by Thase and colleagues, a control group treated with pharmacotherapy was lacking, thereby limiting the validity of the results. Moreover, as only pretreatment HPA axis measures were assessed, an effect of cognitive therapy on HPA axis function cannot be excluded. These two methodological shortcomings have been addressed in a recent study by Yang and associates [147]. The authors demonstrated that in depressed outpatients, a combination of psychotherapy (body–mind–spirit group) and pharmacotherapy was associated with a greater reduction of night-time cortisol levels and a steeper diurnal cortisol pattern, while antidepressant monotherapy (SSRIs or SNRIs) was related to increased salivary cortisol levels and a flatter diurnal cortisol pattern.

Changes in exposure to stressful events, in the available social support systems, in the appraisal of a stressor, in coping resources and changes in health behavior (e.g., sleep, exercise and relaxation) have been identified as possible candidates of psychosocial intervention that could modify HPA axis activity and have an associated risk for depression [143]. Some of these factors have already been under investigation with regard to their potential to alter HPA axis function in healthy human subjects, results of which will be outlined subsequently because of their relevance for psychiatric disorders associated with HPA axis dysfunction.

Concerning social support, it could be demonstrated that the presence of a supportive person reduced the cortisol response to a laboratory psychosocial stressor in healthy adults [148,149]. A series of randomized controlled studies has investigated the effects of cognitive-behavioral stress management (CBSM) on cortisol response to psychosocial stress [150,151]. The CBSM group intervention consisted of a combination of stress-reducing techniques such as cognitive restructuring, problem solving, self-instruction and progressive muscle relaxation. In the first study of the series, a CBSM group intervention for a total of 14 h significantly attenuated cortisol secretion in response to a standardized psychosocial stress test (Trier Social Stress Test) 2 weeks past training in healthy male subjects [150]. This was confirmed by Hammerfald and associates, who found that suppressing effects on cortisol secretion, although being slightly weaker, were even apparent 4 months after a 10-h CBSM training [151]. Interestingly, the differences in cortisol response between groups were partly (20–30%) explained by differences in anticipatory cognitive appraisal. Regarding the stress test as a challenge rather than a threat, a self-concept of high competence and high control expectancy supported by CBSM contributed to a reduced cortisol reaction to the stressor.

To sum up, there is some evidence that HPA axis function can be positively influenced by psychosocial interventions. Previous results suggest that anticipatory stress appraisal is one important factor partially mediating the effects. Further examining psychological processes involved in HPA axis function could help to develop preventive and therapeutic interventions in order to reduce short- and long-term detrimental effects of HPA axis dysregulation [152]. With respect to MDD, future longitudinal studies should investigate if psychotherapeutic interventions already in use (e.g., cognitive behavioural therapy or interpersonal therapy) and CBSM affect HPA axis function by tracing basal HPA axis measures, and measures in response to stress during treatment and follow-up.

Expert commentary

Since the pathogenesis of cognitive decline in depression is not fully understood, investigating the relationship between abnormal neuroendocrine measures and cognitive function in depression is of considerable interest. However, data from correlational and experimental studies reviewed are inconsistent, apparently due to methodological differences. At least 70% of the studies reviewed indicated that there is an association between excessive baseline secretion of GCs or reduced negative feedback and impairment mainly in visual/verbal memory, working memory and executive function in patients with MDD. During the last few decades, neuroendocrine research has made substantial progress in revealing several factors that might mediate the impact of chronically elevated GC levels on cognitive function: abnormalities in the interaction between GCs and the noradrenergic, serotonergic and the immune system leading to an altered function of either system; impaired LTP and neurogenesis by excessive cortisol secretion; dendritic atrophy in the hippocampus and the PFC; reduced (PFC) or enhanced (amygdala) neuronal activation of relevant brain structures; and a GR dysfunction hypothesized to result in a GR/MR imbalance in patients with MDD. There might be many more which have not yet come to light, not to mention their dynamic interplay.

Furthermore, we have highlighted some recent advances of interventions targeting HPA axis abnormalities in MDD patients and healthy human subjects. There is some evidence that anti-GCs, particularly the GR antagonist mifepristone, have an antidepressant effect; however, controlled trials in patients with MDD are absent. Mifepristone has also been found to successfully enhance cognitive function in patients with bipolar disorder, which provides further evidence that

cognitive impairment is strongly related to reduced GR function. It would be of interest to investigate if mifepristone and other anti-GCs serve as potential treatments for cognitive dysfunction in MDD patients. Conventional antidepressants (monoamion-oxidase inhibitors, and serotonin- or norepinephrine-reuptake inhibitors) have been found to increase the binding capacity and expression of GC receptors as well as neurogenesis and expression of BDNF in animal hippocampal neurons. Hence, they might be helpful in restoring HPA axis function and associated cognitive distortions, which was verified for fluoxetine, sertraline and citalopram in two studies with MDD patients. There is also preliminary evidence that HPA axis dysfunction in MDD patients can be altered through psychotherapy. This is of importance for patients known to respond less well to pharmacotherapy, such as MDD patients with a history of early trauma. 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.

In conclusion, an early restoration of normal HPA activity in MDD before the occurrence of structural brain alterations may be an important therapeutic objective. Probably the most effective treatment is a combination of pharmacotherapy and psychotherapy. Therein, anti-GCs might outperform conventional antidepressants in cases with obvious HPA dysregulation. This calls for implementing sensitive HPA axis measures, for example, the DEX/CRH test or prednisolone test, into the diagnostic process.

Five-year view

With regard to its increasing prevalence and debilitating consequences, it is of substantial importance to gain more insight in the etiology of depression and associated cognitive impairment. To this end, a more detailed understanding of the specific molecular mechanisms that underlie cortisol hypersecretion in depressed patients is needed. As most of the data of GC effects on cognition originate from animal studies and data on humans are mostly cross-sectional, more longitudinal studies in humans incorporating structural and functional neuroimaging as well as neuroendocrine parameters and measures of cognitive function are warranted. An important objective for the next 5 years will be to go beyond the HPA axis and focus on the dynamic interplay of GCs within brain structures involved in cognitive performance (i.e., PFC, hippocampus and amygdala). In addition, further longitudinal 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. The goal will be not just to reduce chronically elevated cortisol levels, but to provide the depressed individual with a treatment that helps him/her to regain variability of the stress response that fits situational demands. For this purpose, a better understanding of subgroups of patients with MDD concerning abnormalities of HPA axis function is needed to identify those suffering from hypercortisolism, hypocortisolism or normal HPA axis function with more safety. A challenge to pharmacotherapy will be to identify agents that will not only improve affective symptoms, but also the concomitant neuropsychological impairments. As only approximately 50% of individuals with depression show full remission in response to monoaminergic antidepressants [114], there is also a need for faster acting, safer and more effective treatments for depression. Identification of genetic markers for the prediction of treatment response and relapse would help improving treatment strategies. In the long run, a superior objective will be to develop an integrative and reliable model reconciling the complex interactions of stress with cognition in patients with MDD.

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Key issues

- A significant percentage of patients with major depressive disorder (MDD) show hypothalamic–pituitary–adrenal axis dysregulations, for example, hypercortisolism.
- Glucocorticoid (GC) receptor function seems to be reduced in patients with MDD.
- MDD is associated with cognitive impairments in attention, declarative memory and executive function.
- Chronically elevated GC levels are associated with cognitive impairments in patients with MDD.
- Antiglucocorticoid treatment (e.g., mifepristone) enhances cognitive performance in patients with bipolar disorder.
- Monoaminergic antidepressants (e.g., citalopram and fluoxetine) positively influence hypothalamic–pituitary–adrenal axis function and enhance cognitive performance in patients with MDD.
- Psychotherapy normalizes cortisol secretion in patients with MDD.
- The relationship between GCs and cognition is hypothesized to be reciprocal – GCs affect cognition and cognition affects GCs.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Joels M, Karst H, DeRijk R, de Kloet ER. The coming out of the brain mineralocorticoid receptor. *Trends Neurosci.* 31(1), 1–7 (2007).

2 Roozendaal B, Hernandez A, Cabrera SM *et al.* Membrane-associated glucocorticoid activity is necessary for modulation of long-term memory via chromatin modification. *J. Neurosci.* 30(14), 5037–5046 (2010).

3 Patel PD, Lopez JF, Lyons DM, Burke S, Wallace M, Schatzberg AF. Glucocorticoid and mineralocorticoid receptor mRNA expression in squirrel monkey brain. *J. Psychiatr. Res.* 34, 383–392 (2000).

4 de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat. Rev. Neurosci.* 6(6), 463–475 (2005).

5 Barden N. Implication of the hypothalamic–pituitary–adrenal axis in the physiopathology of depression. *J. Psychiatry Neurosci.* 29(3), 185–193 (2004).

6 Burke HM, Davis MC, Otte C, Mohr DC. Depression and cortisol responses to psychological stress: a meta-analysis. *Psychoneuroendocrinology* 30, 846–865 (2005).

7 Gold PW, Goodwin FK, Chrousos GP. Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (2). *N. Engl. J. Med.* 319(7), 413–420 (1988).

8 Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends Neurosci.* 31, 464–468 (2008).

9 Bhagwagar Z, Hafizi S, Cowen PJ. Increased salivary cortisol after waking in depression. *Psychopharmacology (Berl.)* 183(1), 54–57 (2005).

10 Vreeburg SA, Hoogendijk WJG, van Pelt J *et al.* Major depressive disorder and hypothalamic–pituitary–adrenal axis activity – results from a large cohort study. *Arch. Gen. Psychiatry* 66(6), 617–626 (2009).

11 Holsboer F. The corticosteroid receptor hypothesis of depression. *NeuroPsychopharmacology* 23(5), 477–501 (2000).

•• **Overview of the most important findings concerning the corticosteroid receptor hypothesis of depression.**

12 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* 180, 168–173 (2002).

13 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* 97(1), 325–330 (2000).

14 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* 7, 254–275 (2002).

15 Gold PW, Calabrese JR, Kling MA *et al.* Abnormal ACTH and cortisol responses to ovine corticotropin releasing factor in patients with primary affective disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 10(1), 57–65 (1986).

16 Holsboer F, Gerken A, von Bardeleben U *et al.* Human corticotropin-releasing hormone in depression – correlation with thyrotropin secretion following thyrotropin-releasing hormone. *Biol. Psychiatry* 21(7), 601–611 (1986).

17 Carroll BJ. Dexamethasone suppression test for depression. In: *Frontiers in Biochemical and Pharmacological Research in Depression (Volume 39).* Usdin E. (Ed.). Raven Press, NY, USA, 179–188 (1984).

18 Appelhof BC, Huyser J, Verweij M *et al.* Glucocorticoids and relapse of major depression (dexamethasone/corticotropin-releasing hormone test in relation to relapse of major depression). *Biol. Psychiatry* 59, 696–701 (2006).

19 Nemeroff CB, Evans DL. Correlation between the dexamethasone suppression test in depressed patients and clinical response. *Am. J. Psychiatry* 141(2), 247–249 (1984).

20 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. Psychiatr. Res.* 35, 83–94 (2001).

21 Ising M, Horstmann S, Kloiber S *et al.* Combinded dexamethasone/corticotrophin releasing hormone test predicts treatment response in major depression – a potential biomarker? *Biol. Psychiatry* 62, 47–54 (2007).

22 Young EA, Lopez JF, Murphy-Weinberg V, Watson SJ, Akil H. Mineralocorticoid receptor function in major depression. *Arch. Gen. Psychiatry.* 60, 24–28 (2003).

23 Pariante CM, Papadopoulos AS, Poon L *et al.* A novel prednisolone suppression test for the hypothalamic–pituitary–adrenal axis. *Biol. Psychiatry* 51, 922–930 (2002).

24 Juruena MF, Cleare AJ, Papadopoulos AS, Poon L, Lightman S, Pariante CM. Different responses to dexamethasone and prednisolone in the same depressed patients. *Psychopharmacology (Berl.)* 189, 225–235 (2006).

25 Juruena MF, Pariante CM, Papadopoulos A, Cleare AJ. The development and application of the prednisolone suppression test in psychiatry: a novel tool for assessing glucocorticoid and mineralocorticoid receptor function. *Mind & Brain, J. Psych.* 1(1), 115–122 (2010).

26 Nemeroff CB, Widerlov E, Bisette G *et al.* Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science* 226, 1342–1343 (1984).

27 Calfa G, Kademian S, Ceschin D, Vega G, Rabinovich GA, Volosin M. Characterization and functional significance of glucocorticoid receptors in patients with major depression: modulation by antidepressant treatment. *Psychoneuroendocrinology* 28, 687–701 (2003).

28 Webster MJ, Knable MB, O' Grady J, Orthmann J, Weickert CS. Regional specifity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. *Mol. Psychiatry* 7, 985–994 (2002).

29 Ranga K, Krishnan R, Doraiswamy PM *et al.* Pituitary size in depression. *J. Clin. Endocrinol. Metab.* 72, 256–259 (1991).

30 Nemeroff CB, Krishnan KRR, Reed D, Leder R, Beam C, Dunnick R. Adrenal gland enlargement in major depression. *Arch. Gen. Psychiatry.* 49, 384–387 (1992).

31 De Kloet ER, Vreugdenhil E, Oitzl MS, Joels M. Brain corticosteroid receptor balance in health and disease. *Endocr. Rev.* 19(3), 269–301 (1988).

32 De Kloet ER, DeRijk RH, Meijer OC. Therapy insight: is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression? *Nat. Clin. Pract. Endocrinol. Metab.* 3(2), 168–179 (2007).

33 Van Rossum EFC, Binder EB, Majer M *et al.* Polymorphisms of the glucocorticoid receptor gene and major depression. *Biol. Psychiatry* 59, 681–688 (2006).

34 Otte C, Wüst 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* 34(10), 1574–1581 (2009).

35 Kuningas M, de Rijk RH, Westendorp RG, Jolles J, Slagboom PE, van Heemst D. Mental performance in old age dependent on cortisol and genetic variance in the mineralocorticoid and glucocorticoid receptors. *NeuroPsychopharmacology* 32, 1295–1301 (2007).

36 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 4th edition.* American Psychiatric Publishing, Washington, DC, USA (1994).

37 Beblo T, Lautenbacher S. [*Neuropsychology of depression*]. Hogrefe, Göttingen, Germany (2006).

38 Chamberlain SR, Sahakian BJ. The neuropsychology of mood disorders. *Curr. Psychiatry Rep.* 8, 458–463 (2006).

39 Porter RJ, Bourke C, Gallagher P. Neuropsychological impairment in major depression: its nature, origin and clinical significance. *Aust. NZ J. Psychiatry* 41, 115–128 (2007).

40 Christensen H, Griffiths K, Mackinnon A, Jacomb P. A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *J. Int. Neuropsychol. Soc.* 3(6), 631–651 (1997).

41 Leppanen JM. Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Curr. Opin Psychiatry* 19(1), 34–39 (2006).

42 Henry J, Crawford JR. A meta-analytic review of verbal fluency deficits in depression. *J. Clin. Exp. Neuropsychol.* 27(1), 78–101 (2005).

43 Gorwood P, Corruble E, Falissard B, Goodwin GM. Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *Am. J. Psychiatry* 165(6), 731–739 (2008).

44 Williams JMG, Barnhofer T, Crane C *et al.* Autobiographical memory specifity and emotional disorder. *Psychol. Bull.* 133(1), 122–148 (2007).

45 Gualtieri CT, Johnson LG. Age-related cognitive decline in patients with mood disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 32(4), 962–967 (2008).

46 Douglas KM, Porter R J. Longitudinal assessment of neuropsychological function in major depression. *Aust. NZ J. Psychiatry* 43(12), 1105–1117 (2009).

47 Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct. Funct.* 213(1–2), 93–118 (2008).

48 Lorenzetti V, Allen NB, Fornito A, Yucel M. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. *J. Affect. Disord.* 117(1–2), 1–17 (2009).

49 de Kloet ER, Oitzl MS, Joels M. Stress and cognition: are corticosteroids good or bad guys? *Trends Neurosci.* 22(10), 422–426 (1999).

50 Belanoff JK, Gross K, Yager A, Schatzberg AF. Corticosteroids and cognition. *J. Psychatr. Res.* 35, 127–145 (2001).

51 de Quervain DJF, Aerni A, Schelling G, Roozendaal B. Glucocorticoids and the regulation of memory in health and disease. *Front. Neuroendocrinol.* 30, 358–370 (2008).

•• **Summarizes the most important findings on the impact of glucocorticoids on cognition.**

52 Het S, Ramlow G, Wolf OT. A meta-analytic review of the effects of acute cortisol administration on human memory. *Psychoneuroendocrinology* 30, 771–784 (2005).

53 Lupien SJ, Maheu F, Tu M, Fiocco A, Schramek TE. The effects of stress and stress hormones on human cognition: implications for the field of brain and cognition. *Brain Cogn.* 65, 209–237 (2007).

54 Sandi C, Pinelo-Nava MT. Stress and memory: behavioural effects and neurobiological mechanisms. *Neural Plast.* 1–20 (2007).

55 Joels M, Pu Z, Wiegert O, Oitzl MS, Krugers HJ. Learning under stress: how does it work? *Trends Cogn. Sci.* 10, 152–158 (2006).

56 Roozendaal B. Stress and memory: opposing effects of glucocorticoids on memory consolidation and memory retrieval. *Neurobiol. Learn. Mem.* 78, 578–595 (2002).

57 Wolf OT. Stress and memory in humans: twelve years of progress? *Brain Res.* 1293, 142–154 (2009).

58 Wolf OT. The influence of stress hormones on emotional memory: relevance for psychopathology. *Acta Psychol. (Amst.)* 127(3), 513–531 (2008).

59 Tulving E. Organization of memory: *quo vadis*? In: *The Cognitive Neurosciences.* Gazzangia MS (Ed.). MIT Press, Cambridge, UK, 839–847 (1995).

60 Baddeley A. Working memory. *Science* 255, 556–559 (1992).

61 Newcomer JW, Sella H, Melson AK. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Arch. Gen. Psychiatry* 56, 527–533 (1999).

62 Newcomer JW, Craft S, Hershey T, Askins K, Bardgett ME. Glucocorticoid-induced impairment in declarative memory performance in adult humans. *J. Neurosci.* 14(4), 2047–2053 (1994).

63 Kirschbaum C, Wolf OT, May M, Wippich W, Hellhammer DH. Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sciences* 58(17), 1475–1483 (1996).

64 Wolf OT, Convit A, McHugh PF *et al.* Cortisol differentially affects memory in young and elderly men. *Behav. Neurosci.* 115(5), 1002–1011 (2001).

65 Buchanan TW, Lovallo WR. Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology* 26, 307–317 (2001).

66 Cahill L, Gorski L, Le K. Enhanced human memory consolidation with post-learning stress: interaction with the degree of arousal at encoding. *Learn. Mem.* 10, 270–274 (2003).

67 Kuhlmann S, Wolf OT. Arousal and cortisol interact in modulating memory consolidation in healthy young men. *Behav. Neurosci.* 120, 217–223 (2006).

68 Abercrombie HC, Kalin NH, Thurow ME, Rosenkranz MA, Davidson RJ. Cortisol variation in humans affects memory for emotionally laden and neutral information. *Behav. Neurosci.* 117, 505–516 (2003).

69 Rimmele U, Domes G, Mathiak K, Hautzinger M. Cortisol has different effects on human memory for emotional and neutral stimuli. *Neuroreport* 14, 2485–2488 (2003).

70 Lupien S, Gillin CJ, Hauger RL. Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: a dose–response study in humans. *Behav. Neurosci.* 113(3), 420–430 (1999).

71 Young AH, Sahakian BJ, Robbins TW. The effects of chronic administration of hydrocortisone on cognitive function in normal volunteers. *Psychopharmacology* 145, 260–266 (1999).

72 Schoofs D, Preuss D, Wolf OT. Psychosocial stress induces working memory impairments in an n-back paradigm. *Psychoneuroendocrinology* 33, 643–653 (2008).

73 Kuhlmann S, Kirschbaum C, Wolf OT. Effects of oral cortisol treatment in healthy young women on memory retrieval of negative and neutral words. *Neurobiol. Learn. Mem.* 83, 158–162 (2005).

74 Kuhlmann S, Piel M, Wolf OT. Impaired memory retrieval after psychosocial stress in healthy young men. *J. Neurosci.* 25 (11), 2977–2982 (2005).

75 Buss C, Wolf OT, Witt J, Hellhammer DH. Autobiographic memory impairment following acute cortisol administration. *Psychoneuroendocrinology* 29, 1093–1096 (2004).

76 Roozendaal B, Okuda S, de Quervain DJ, McGaugh JL. Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. *Neuroscience* 138, 901–910 (2006).

77 Pavlides C, Watanabe Y, McEwen BS. Effects of glucocorticoids on hippocampal long-term potentiation. *Hippocampus* 3, 183–192 (1993).

78 de Quervain DJ, Henke K, Aerni A *et al.* Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. *Eur. J. Neurosci.* 17, 1296–1302 (2003).

79 Oei NYL, Elzinga BM, Wolf OT *et al.* Glucocorticoids decrease hippocampal and prefrontal activation during declarative memory retrieval in young men. *Brain Imaging Behav.* 1, 31–41 (2007).

80 Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* 9, 46–56 (2008).

81 Herbert J, Goodyer IM, Grossman AB *et al.* Do corticosteroids damage the brain? *J. Neuroendocrinol.* 18, 393–411 (2006).

82 Vythilingam M, Heim C, Newport J *et al.* Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am. J. Psychiatry* 159(12), 2072–2080 (2002).

83 Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with major depression. *J. Neurosci.* 19, 5034–5043 (1999).

84 Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. *Proc. Natl Acad. Sci. USA* 93(9), 3908–3913 (1996).

85 Paizanis E, Hamon M, Lanfumey L. Hippocampal neurogenesis, depressive disorders, and antidepressant therapy. *Neural Plast.* 737–754 (2007).

86 Becker S, Macqueen G, Wojtowicz JM. Computational modeling and empirical studies of hippocampal neurogenesis-dependent memory: effects of interference, stress and depression. *Brain Res.* 1299, 45–54 (2009).

87 Kelly WF, Checkley SA, Bender DA, Mashiter K. Cushing's syndrome and depression – a prospective study of 26 patients. *Br. J. Psychiatry* 142, 16–19 (1983).

88 Starkman MN, Giordani B, Berent S, Schork MA, Schteingart DE. Elevated cortisol levels in Cushing's disease are associated with cognitive decrements. *Psychosom. Med.* 63, 985–993 (2001).

89 Bremner JD, Vythilingam M, Vermetten E, Anderson G, Newcomer JW, Charney DS. Effects of glucocorticoids on declarative memory function in major depression. *Biol. Psychiatry* 55, 811–815 (2004).

90 Schlosser N, Wolf OT, Carvalho Fernando S *et al.*. Effects of acute cortisol administration on autobiographical memory in patients with major depression and healthy controls. *Psychoneuroendocrinology* 35, 316–320 (2010).

• **First experimental study demonstrating evidence for a reduced central glucocorticoid sensitivity in patients with major depressive disorder.**

91 Rubinow DR, Post RM, Savard R, Gold PW. Cortisol hypersecretion and cognitive impairment in depression. *Arch. Gen. Psychiatry* 41, 279–283 (1984).

92 Wauthy J, Ansseau M, von Frenckell R, Mormont C, Legros JJ. Memory disturbances and dexamethasone suppression test in major depression. *Biol. Psychiatry* 30, 736–738 (1991).

93 Sikes CR, Stokes PE, Lasley BJ. Cognitive sequelae of hypothalamic–pituitary–adrenal (HPA) dysregulation in depression. *Biol. Psychiatry* 25, 148A–152A (1989).

94 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.* 112, 434–441 (2005).

95 Gomez R, Fleming SH, Keller J *et al.* The neuropsychological profile of psychotic major depression and its relation to cortisol. *Biol. Psychiatry* 60, 472–478 (2006).

96 van Londen L, Goekoop JG, Zwindermann AH, Lanser JBK, Wiegant VM, de Wied D. Neuropsychological performance and plasma cortisol, arginine vasopressin and oxytocin in patients with major depression. *Psychol. Med.* 28, 275–284 (1998).

97 Michopoulos I, Zervas IM, Pantelis C *et al.* Neuropsychological and hypothalamic–pituitary-axis function in female patients with melancholic and non-melancholic depression. *Eur. Arch. Psychiatry Clin. Neurosci.* 258, 217–225 (2008).

98 Belanoff JK, Kalehzan M, Sund B, Fleming Ficek SK, Schatzberg, AF. Cortisol activity and cognitive changes in psychotic major depression. *Am. J. Psychiatry* 158, 1612–1616 (2001).

99 Barnhofer T, Kuehn EM, de Jong-Meyer R. Specifity of autobiographical memories and basal cortisol levels in patients with major depression. *Psychoneuroendocrinology* 30, 403–411 (2005).

100 den Hartog HM, Nicolson NA, Derix MMA, van Bemmel AL, Kremer B, Jolles J. Salivary cortisol patterns and cognitive speed in major depression: a comparison with allergic rhinitis and healthy control subjects. *Biol. Psychol.* 63, 1–14 (2003).

101 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. *Psychoneuroendocrinology* 34, 1012–1018 (2009).

102 Hinkelmann K, Moritz S, Botzenhardt J *et al.* Cognitive impairment in major depression: association with salivary cortisol. *Biol. Psychiatry* 66, 879–885 (2009).

• **Well-designed study demonstrating a negative association between cortisol level and cognitive function in patients with major depressive disorder.**

103 Mannie ZN, Barnes J, Bristow GC, Harmer CJ, Cowen PJ. Memory impairment in young women at increased risk of depression: influence of cortisol and 5-HTT genotype. *Psychol. Med.* 39, 757–762 (2009).

104 Holsboer F, Lauer CJ, Schreiber W, Krieg JC. Altered hypothalamic–pituitary–adrenocortical regulation in healthy subjects at high familial risk for affective disorders. *Neuroendocrinology* 62, 340–347 (1995).

105 Modell S, Lauer CJ, Schreiber W, Huber J, Krieg JC, Holsboer F. Hormonal response pattern in the combined DEX-CRH test is stable over time in subjects at high familial risk for affective disorders. *Neuropsychopharmacology* 18, 253–262 (1998).

106 Vythilingam M, Vermetten E, Anderson GM *et al.* Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. *Biol. Psychiatry* 56, 101–112 (2004).

107 Brown WA, Qualls CB. Pituitary–adrenal disinhibition in depression: marker of a subtype with characteristic clinical features and response to treatment? *Psychiatr. Res.* 4, 115–128 (1981).

108 Winokur G, Black DW, Nasrallah A. DST nonsuppressor status: relationship to specific aspects of the depressive syndrome. *Biol. Psychiatry* 22, 360–368 (1987).

109 Caine ED, Yerevanian BI, Bamford KA. Cognitive function and the dexamethasone suppression test in depression. *Am. J. Psychiatry* 141, 116–118 (1984).

110 Wolkowitz OM, Reus VI, Weingartner H *et al.* Cognitive effects of corticosteroids. *Am. J. Psychiatry* 147, 1297–1303 (1990).

111 Zobel AW, Schulze-Rauschenbach S, von Widdern OC *et al.* Improvement of working but not declarative memory is correlated with HPA normalization during antidepressant treatment. *J. Psychiatr. Res.* 38, 377–383 (2004).

112 Reppermund S, Zihl J, Lucae S. Persistent cognitive impairment in depression: the role of psychopathology and altered hypothalamic–pituitary–adrenocortical (HPA) system regulation. *Biol. Psychiatry* 62, 400–406 (2007).

113 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* 194(4), 342–349 (2009).

114 Kaufmann J, Charney D. Effects of early stress on brain structure and function: implications for understanding the relationship between child maltreatment and depression. *Dev. Psychopathol.* 13, 451–471 (2001).

115 Hammen CL. Stress and depression. In: *Annual Review of Clinical Psychiatry (Volume 1)*. Annual Reviews, Palo Alto, CA, USA, 293–319 (2005).

116 Monroe SM, Hadjiyannakis KL. The social environment and depression: focusing on severe life stress. In: *Handbook of Depression*. Gotlib IH, Hammen CL (Eds). Guilford Press, NY, USA, 314–340 (2002).

117 Starkman MN, Schteingart DE, Schork MA. Cushing's syndrome after treatment: changes in cortisol and ACTH levels, and amelioration of the depressive syndrome. *Psychiatry Res.* 19, 177–188 (1986).

118 Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. *Nat. Neurosci.* 7, 137–151 (2006).

119 Kling MA, Coleman VH, Schulkin J. Glucocorticoid inhibition in the treatment of depression: can we think outside the endocrine hypothalamus? *Depress. Anxiety* 26, 641–649 (2009).

120 Porter RJ, Gallagher P. Abnormalities of the HPA axis in affective disorders: clinical subtypes and potential treatments. *Acta Neuropsychiatrica* 18, 193–209 (2006).

121 Schüle C, Baghai TC, Eser D, Rupprecht R. Hypothalamic–pituitary–adrenocortical system dysregulation and new treatment strategies in depression. *Expert Rev. Neurother.* 9(7), 1005–1019 (2009).

- **Most up-to-date review on the use of antiglucocorticoid pharmacotherapy in the treatment of depression.**

122 Thomson F, Craighead M. Innovative approaches for the treatment of depression: targeting the HPA axis. *Neurochem. Res.* 33, 691–707 (2008).

123 Gallagher P, Malik N, Newham J, Young AH, Ferrier IN, Mackin P. Antiglucocorticoid treatments for mood disorders. *Cochrane Database Syst. Rev.* 1, CD005168 (2008).

124 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* 29, 1538–1545 (2004).

- **First study indicating a positive effect of antiglucocorticoid pharmacotherapy on cognitive function in mood disorders.**

125 Mason BL, Pariante CM. The effects of antidepressants on the hypothalamic–pituitary–adrenal axis. *Drug News Perspect.* 19(10), 603–608 (2006).

126 Schüle C. Neuroendocrinological mechanisms of actions of antidepressant drugs. *J. Neuroendocrinol.* 19, 213–226 (2006).

127 Brady LS, Whitfield HJ Jr, Fox RJ, Gold PW, Herkenham M. Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineralocorticoid receptor gene expression in rat brain. Therapeutic implications. *J. Clin. Invest.* 87, 831–837 (1991).

128 Seckl JR, Fink G. Antidepressants increase glucocorticoid and mineralocorticoid receptor mRNA expression in rat hippocampus *in vivo*. *Neuroendocrinology* 55, 621–626 (1992).

129 Reul JM, Stee I, Soder M, Holsboer F. Chronic treatment of rats with the antidepressant amitriptyline attenuates the activity of the hypothalamic–pituitary–adrenocortical system. *Endocrinology* 133, 312–320 (1993).

130 Reul JM, Labeur MS, Grigoriadis DE, De Souza EB, Holsboer F. Hypothalamic–pituitary–adrenocortical axis changes in the rat after long-term treatment with the reversible monoamine oxidase-A inhibitor moclobemide. *Neuroendocrinology* 60, 509–519 (1994).

131 Yau JL, Olsson T, Morris RG, Meaney MJ, Seckl JR. Glucocorticoids, hippocampal corticoid receptor gene expression and antidepressant treatment: relationship with spatial learning in young and aged rats. *Neuroscience* 66, 571–581 (1995).

132 Carvalho LA, Pariante CM. *In vitro* modulation of the glucocorticoid receptor by antidepressants. *Stress* 11(6), 411–424 (2008).

133 Otte C, Hinkelmann K, Moritz S. Modulation of the mineralocorticoid receptor as add-on treatment in depression: a randomized, double blind, placebo-controlled proof-of-concept study. *J. Psychiatr. Res.* 44(6), 339–346 (2010).

134 Juruena MF, Gama CS, Berk M, Belmonte-de-Abreu PS. Improved stress response in bipolar affective disorder with adjunctive spironolactone (mineralocorticoid receptor antagonist): case series. *J. Psychopharmacol.* 23, 985–987 (2009).

135 López JF, Chalmers DT, Little KY, Watson SJ. Regulation of serotonin 1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. *Biol. Psychiatry* 43, 547–573 (1998).

136 McKay MS, Zakzanis KK. The impact of treatment on HPA axis activity in unipolar major depression. *J. Psychiatr. Res.* 44, 183–192 (2010).

137 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* 56, 113–120 (2004).

138 Watson S, Gallagher P, Del-Estal D, Hearn A, Ferrier IN, Young AH. Hypothalamic–pituitary–adrenal axis function in patients with chronic depression. *Psychol. Med.* 32, 1021–1028 (2002).

139 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. *PNAS* 100(24), 14293–14296 (2003).

140 Heim C, Plotsky PM, Nemeroff CB. Importance of studying the contributions of adverse early experience to neurobiological findings in depression. *Neuropsychopharmacology* 29, 641–648 (2004).

141 Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB. The dexamethasone/corticotrophin-releasing factor test in men with major depression: role of childhood trauma. *Biol. Psychiatry* 63(4), 398–405 (2008).

142 Adam EK, Hawkley LC, Kudielka BM, Cacioppo JT. Day-to-day dynamics of experience cortisol associations in a population-based sample of older adults. *Proc. Natl Acad. Sci. USA* 103, 17058–17063 (2006).

143 Adam EK, Sutton JM, Doane LD, Mineka S. Incorporating hypothalamic–pituitary–adrenal axis measures into preventive interventions for adolescent depression: are we there yet? *Dev. Psychopathol.* 20, 975–1001 (2008).

144 Hawley LL, Ho MHR, Zuroff DC, Blatt SJ. Stress reactivity following brief treatment for depression: differential effects of psychotherapy and medication. *J. Consult. Clin. Psychol.* 75(2), 244–256 (2007).

145 Thase ME, Dubé S, Bowler K *et al.* Hypothalamic–pituitary–adrenocortical acitivity and response to cognitive behaviour therapy in unmedicated, hospitalized depressed patients. *Am. J. Psychiatry* 153 (7), 886–891 (1996).

146 Schwabe L, Wolf OT. Stress prompts habit behavior in humans. *J. Neurosci.* 29(22), 7191–7198 (2009).

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. Nerv. Ment. Dis.* 197 (6), 401–406 (2009).

• **First study demonstrating a positive effect of psychotherapy on hypothalamic–pituitary–adrenal axis function in patients with major depressive disorder.**

148 Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol. Psychiatry* 54, 1389–1398 (2003).

149 Kirschbaum C, Klauer T, Filipp SH, Hellhammer DH. Sex-specific effects of social support on cortisol and subjective responses to acute psychosocial stress. *Psychosom. Med.* 57, 23–31 (1995).

150 Gaab J, Blattler N, Menzi T, Pabst B, Stoyer S, Ehlert U. Randomized controlled evaluation of the effects of cognitive-behavioral stress management on cortisol responses to acute stress in healthy subjects. *Psychoneuroendocrinology* 28, 767–779 (2003).

151 Hammerfald K, Eberle C, Grau M, Kinsperger A, Zimmermann A, Ehlert U. Persistent effects of cognitive-behavioral stress management on cortisol responses to acute stress in healthy subjects – a randomized controlled trial. *Psychoneuroendocrinology* 31, 333–339 (2006).

152 Ursin H, Erikson HR. The cognitive activation theory of stress. *Psychoneuroendocrinology* 29, 567–592 (2004).