



Effects of cortisol on cognition in major depressive disorder, posttraumatic stress disorder and borderline personality disorder - 2014 Curt Richter Award Winner



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Abstract Stress hormones influence a wide range of cognitive functions, including memory performance and executive function. It is well established that glucocorticoids enhance memory consolidation but impair memory retrieval. While most of the effects have been attributed to glucocorticoid receptors (GR), the importance of mineralocorticoid receptors (MR) has been also emphasized.

Dysfunctions in hypothalamic–pituitary–adrenal (HPA) axis have been reported for several mental disorders. While major depressive disorder (MDD) as well as borderline personality disorder (BPD) seem to be characterized by enhanced cortisol release in concert with a reduced feedback sensitivity of the HPA axis, in posttraumatic stress disorder (PTSD) a contrary picture has been reported. Despite the fact that altered GR function has been discussed for these disorders only very few studies have investigated the effects of glucocorticoids on cognitive performance in these patients so far.

In a series of studies, we investigated the effects of glucocorticoids on cognition (i.e. declarative memory, working memory and response inhibition) in different mental disorders such as MDD, PTSD and BPD. While in patients with MDD cortisol administration failed to effect memory retrieval, patients with PTSD and BPD showed enhanced rather than impaired memory retrieval after cortisol administration. These results indicate an altered sensitivity to cortisol in these disorders. Results from one of our recent studies in the field of social cognition underline the importance of the MR. We found that emotional empathy was enhanced through stimulation of the MR via fludrocortisone in healthy participants and women with BPD. This review aims to integrate these findings and discuss potential mechanisms and implications.

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1. Introduction

Stress, including (early) traumatic experiences, has been associated with a higher risk of a wide range of mental disorders, such as major depressive disorder, anxiety disorders, eating disorders, somatoform disorders and personality disorders. Therefore, many studies have investigated the functioning of the hypothalamic–pituitary–adrenal (HPA) axis in these disorders. Briefly, upon stress exposure, corticotropin-releasing factor (CRF) is released from the hypothalamus which works in conjunction with arginine vasopressin (AVP) to stimulate the secretion of adrenocorticotropin (ACTH) (Holsboer and Ising, 2010). ACTH in turn stimulates the synthesis and release of glucocorticoids (GCs) from the adrenal cortex. The neuroendocrine stress response is regulated by circulating GCs via negative feedback mechanisms targeting the pituitary, hypothalamus, and hippocampus. This negative feedback loop is essential for the regulation of the HPA axis and the regulation of the stress response (de Kloet et al., 2005). GCs mediate their effects by binding to two subtypes of intracellular receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). These two receptors differ in their affinity and distribution within the brain (de Kloet et al., 2005): while MR are mainly located in the hippocampus, GR are expressed throughout the brain, e.g. the prefrontal cortex (Lupien and Lepage, 2001; de Kloet et al., 2005). In addition, also membrane-bound GR and MR have been identified (Joels et al., 2008; Roozendaal et al., 2010). Due to their prominence throughout the brain, corticoid receptors modulate several cognitive processes, including memory. While most of the effects associated with GCs – especially when related to stress – have been attributed to GR, the importance of mineralocorticoid receptors (MR) has been also emphasized (Reul et al., 2000; Joels et al., 2008; de Kloet, 2013).

It is well established that in healthy participants memory consolidation is enhanced by cortisol, whereas long-term memory retrieval is impaired after GC administration (Wolf, 2009). Similar effects on memory retrieval have been obtained after psychosocial laboratory stressors. The impairing effects of cortisol have also been found for autobiographic memory retrieval (Buss et al., 2004; Young et al., 2011) and working memory (e.g. Lupien et al., 1999; Wolf et al., 2001), although not all studies agree (Monk and Nelson, 2002; Porter et al., 2002; Oei et al., 2009). Effects of acute cortisol elevation on inhibitory control were investigated only in a few studies. Scholz et al. (2009) for example demonstrated that a psychosocial stress induction impaired go/no-go performance. In contrast, Zwissler et al. (2011) found inhibitory control of memory in a directed forgetting task not to be affected after a psychosocial stress. Using acute cortisol administration, Wolf et al. (2001) found no impairing effect of on performance in a Stroop task. Oei et al. (2009) even found an enhancing effect of cortisol on inhibitory performance when examining distracter interference in a Sternberg working memory task.

At this point it has to be emphasized that exposure to (psychosocial) stress and administration of cortisol differ markedly in several endocrine aspects: while stress exposure leads to centrally increased CRF, AVP and peripherally induced corticosteroids that penetrate into the brain, exogenous cortisol, enters the brain and decreases CRF and

AVP. Thus, different and even opposite effects on cognition might occur. In contrast if both approaches induce highly similar behavioural consequences an important role of cortisol in mediating the observed effects appears likely. In the context of memory retrieval the effects of stress induced cortisol increases and exogenously administered cortisol are highly similar. Given the neuroendocrine differences between these two states this supports our conclusion that indeed cortisol is the driving factor in both scenarios (since CRH, AVP and ACTH differ).

Most of the mentioned studies used stress exposure or cortisol administration which leads to a stimulation of both glucocorticoid receptor types, GR and MR. However, some studies had a closer look at the role of the MR in terms of cognition. Indeed, it has been consistently shown that blocking the MR e.g. with spironolactone leads to impaired cognitive function in humans (Otte et al., 2007; Cornelisse et al., 2011; Rimmele et al., 2013). Interestingly, these impairing effects of MR blockade were most pronounced for emotional memory (Rimmele et al., 2013). Of note spironolactone also leads to decreases in blood pressure, which makes it difficult to clearly differentiate its MR effects from effects possibly triggered by blood pressure. However, as studies which investigated the effects of MR blockade on memory use relatively low dosages of spironolactone, effects on blood pressure and heart rate are not seen in these investigations (Otte et al., 2007; Cornelisse et al., 2011). Thus, it seems to be likely that the observed effects on cognition are indeed associated with MR function.

Alterations of the HPA axis have been reported for a wide range of mental disorders, including major depressive disorder (MDD), posttraumatic stress disorder (PTSD) and borderline personality disorder (BPD). While MDD as well as BPD seem to be characterized by enhanced cortisol release in concert with a reduced feedback sensitivity of the HPA axis, in PTSD a contrary picture has been reported (Yehuda, 2002; Parker et al., 2003; Wingenfeld et al., 2010). Recent studies also investigated the functioning of the GR directly in MDD (McGowan et al., 2009) as well as in PTSD (Rohleder et al., 2004). Of note, findings of HPA axis dysregulations in mental disorder are far from homogenous (Nemeroff, 2002; Nestler et al., 2002; Meewisse et al., 2007; Heim and Nemeroff, 2009; Wingenfeld et al., 2010). Despite the fact that altered GR functioning has been discussed for these disorders, only very few studies have investigated the effects of GCs on cognitive performance in these patients so far (Wingenfeld and Wolf, 2011).

In a series of studies, we investigated the effects of cortisol (10 mg hydrocortisone orally) on cognition, i.e. declarative memory, working memory and response inhibition, in mental disorders such as MDD, PTSD and BPD. We used the same tasks for all patient groups to be able to compare the results. In addition to a word list learning (consisting of 21 words), an autobiographical memory test was used (Buss et al., 2004). Patients with overgeneralized memory have difficulties in retrieving specific autobiographical events. Instead, they tend to reply with abstract or general memory content (e.g. they summarize several different events). To test the verbal modality of working memory, we used the self-developed Word Suppression Test (WST) in the style of the Wechsler Memory Scale. The WST consisted of two test parts - one with negative and one with neutral

interference words (Terfehr et al., 2011a,b). Finally, an emotional go/no-task was used to evaluate the effects of cortisol on response inhibition (Carvalho Fernando et al., 2013; Schlosser et al., 2013). In a very recent study, we extended our research on the effects of MR stimulation to social cognition, i.e. cognitive and emotional empathy in BPD patients (Wingenfeld et al., 2014).

In the following, we will summarize and integrate these findings and discuss potential mechanisms and implications.

2. Major depressive disorder

2.1. Clinical features and HPA axis alterations

MDD is one of the most prevalent mental disorders. It has become a major health problem and is ranked among the leading causes of disability worldwide. Biological, psychological, and social factors are known to play a role in the development of MDD, suggesting that depression develops when a pre-existing vulnerability, or diathesis, is activated by stressful life events (Heim et al., 2008). A major depressive episode is characterized by depressed mood and/or loss of interest or pleasure accompanied by sleep disturbances, psychomotor agitation or retardation, fatigue and loss of energy, feelings of worthlessness, excessive or inappropriate guilt, as well as recurrent thoughts of death or suicide or even suicide attempt. Cognitive disturbances as lack of concentration and indecisiveness are also core symptoms of MDD. A substantial amount of studies using neuropsychological assessment has shown that attention, declarative memory and executive function are impaired in MDD (Chamberlain and Sahakian, 2006). Furthermore, studies investigating autobiographical memory have consistently 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 (Williams et al., 2007).

Dysregulations of the HPA axis are a prominent finding in MDD. In about 50–70% of the patients, functional abnormalities of the HPA axis, including cortisol hypersecretion (Parker et al., 2003) and a reduced peripheral GR sensitivity (Holsboer, 2000), have been found. One important finding is that cortisol levels after dexamethasone (DEX) administration are less suppressed in MDD (Ising et al., 2005). This reduced feedback sensitivity has been interpreted as reflecting an exaggerated CRF drive (Nemeroff, 1996) and/or as a reduction of GR functioning (Holsboer, 2000). Post-mortem studies support this hypothesis by reporting a reduced GR mRNA in depressed patients (Webster et al., 2002). Furthermore, an increased methylation of the GR gene promoter inhibiting GR expression (McGowan et al., 2009) has been found. GR gene polymorphisms are also discussed to be associated with depression (Binder et al., 2004; Otte et al., 2009b; Spijker and van Rossum, 2012; Koper et al., 2014). Interestingly, some polymorphisms of the GR are discussed to be associated with cognitive function such as working memory (Kumsta et al., 2010). In females with a specific polymorphism (heterozygous carriers of the 9 beta G allele) was associated with faster reaction times in response to cortisol which was not seen in men. Interestingly, in this

polymorphism was also associated with relative GR resistance (Kumsta et al., 2007).

As mentioned before the mineralocorticoid receptor also plays an important role in the regulation of the HPA axis and the coordination of the stress response (Reul et al., 2000; Gesing et al., 2001). While the GR has been at the focus of most earlier studies examining neuroendocrine pathways of MDD, there is also evidence that MR dysfunction might play a role (de Kloet et al., 2005; Otte et al., 2009a; Rohleder et al., 2009). In light of the MR/GR balance model of depression (de Kloet, 2013), combined investigations of both receptors are required.

In sum, the results of abnormal HPA axis functioning in patients with MDD have generally been interpreted as reflecting an exaggerated CRF drive and/or reduced GR functioning. Additionally, a shift of MR/GR balance might also play an important role in this process. Although it is still a matter of debate, GR and/or MR function and genetic variations of them appear to be important factors in the pathogenesis of MDD.

2.2. Cortisol and cognition in MDD

As MDD is characterized not only by HPA axis dysregulations but also cognitive impairments several studies investigated the association between HPA axis functioning and memory performance in these patients. Some studies found associations between cortisol levels and cognitive impairment, predominantly in depressed patients with psychotic symptoms, but other studies failed to find such associations (see Schlosser et al., 2011 for review). In one of our own studies, we found a negative correlation between the cortisol awakening response (CAR) and memory function in depressed patients (Hinkelmann et al., 2013). Of note, the CAR is thought to reflect the sensitivity of the HPA axis and, thus, might be a more sensitive marker for the association of HPA axis (re-) activity and cognition compared to basal cortisol levels. However, the cross-sectional and correlative design of these studies renders them inconclusive with regard to causality.

To our knowledge, only one study has investigated the effect of GC administration on memory in MDD (Bremner et al., 2004a,b). Bremner and colleagues found that two days of 2 mg DEX treatment improved episodic memory in patients with MDD. The authors suggested that a reduction of cortisol after DEX might have led to the observed memory improvement.

In our research group, we investigated the effect of a single administration of 10 mg hydrocortisone on several neuropsychological domains in MDD. In a declarative memory task, i.e. a word list leaning paradigm, we could replicate the impairing effect of cortisol on memory retrieval in healthy participants (de Quervain et al., 2000; Wolf et al., 2001), while there was no effect in MDD patients (Terfehr et al., 2011a,b) (see Fig. 1A). A similar pattern was found in an autobiographical memory test: acute cortisol administration impaired autobiographical memory performance in healthy controls, but not in MDD patients (Schlosser et al., 2010) (see Fig. 1B). These results indicate that hippocampus based declarative memory retrieval was not affected by cortisol administrations in MDD patients.

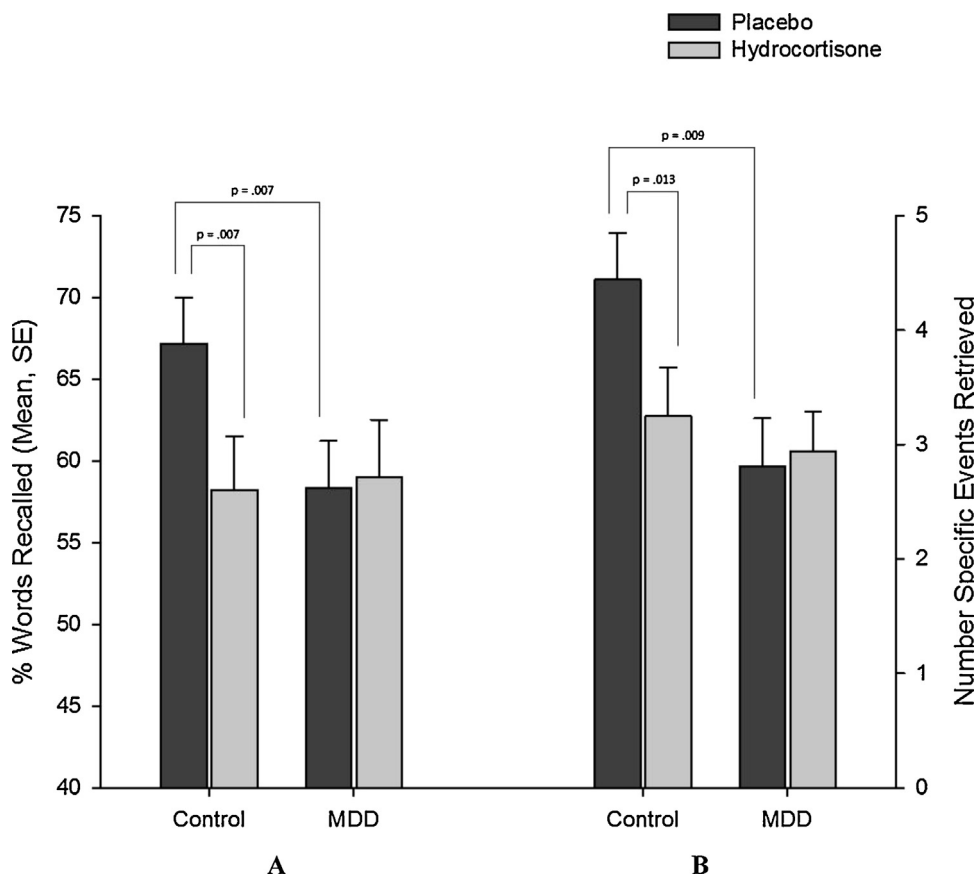


Fig. 1 The effects of 10 mg hydrocortisone on (A) percentage of words retrieved in the word list paradigm in relation to the learning list on the previous day (mean [SE]) and (B) on autobiographic memory retrieval (number of specific events retrieved; mean [SE]) in patients with MDD in comparison to sex and age-matched healthy controls. Adapted from: Schlosser et al., 2010 *Psychoneuroendocrinology*, 37, 1048–1056 and Terfehr et al., 2011a,b, *Journal of Clinical Psychiatry*, 72 (12), 1644–1650.

One of the major cognitive impairments in MDD has been found in PFC mediated executive functions (Rogers et al., 2004). Thus, we further aimed to investigate whether the finding of missing effects of acute cortisol administration on memory performance in MDD also apply for prefrontal-based working memory. Using a digit span task which includes two test parts (one with negative and one with neutral interference words), we found that healthy participants showed a significantly poorer working memory performance after cortisol intake compared to placebo treatment when negative interference words were presented. In the neutral test part no such effect was seen. This result is in line with a study that found impairing stress effects for WM at high loads, but not at low loads (Oei et al., 2006). In contrast, memory performance in MDD patients was not affected by cortisol treatment neither in the neutral nor in the negative test part (Terfehr et al., 2011a,b). Another key component of executive functions is referred to as 'inhibitory control' which allows inhibiting the processing of irrelevant information. In a recently published study, we could show that cortisol administration had an enhancing effect on inhibitory performance in a go/no-go task in healthy control participants, indicated by faster responses. A similar finding has been also reported by Schwabe et al. (2013). In MDD patients, no effect of cortisol on task performance was revealed (Schlosser et al., 2013) (see Fig. 2). Still, cognitive

performance in all tasks was worse in the MDD group compared to healthy control participants as expected (see also Figs. 1 and 2).

Our sample of depressed patients also includes patients with antidepressive medication but we did not see any difference concerning cognitive performance in their response to cortisol between those with compared to those without medication intake (Terfehr et al., 2011a,b). As sample size for these subgroup analyses were rather small more research is needed to investigate the interaction between antidepressive medication and stress hormones on cognition.

In sum, we could replicate that cortisol administration impairs declarative memory retrieval and working memory performance in healthy controls while it enhances inhibitory performance. In contrast, in patients with MDD no effect of cortisol on any cognitive domain could be seen. We discuss the missing impairing GC effects in MDD patients with regard to the reduced GR sensitivity in MDD. Several investigations support this hypothesis. Using the dexamethasone suppression test and the combined DEX/CRF test in MDD, a reduced feedback sensitivity of the HPA axis was shown and has been interpreted as reduction of GR functioning (Holsboer, 2000). In this context vasopressin has been also emphasized to play an important role in MDD (Scott and Dinan, 1998; Newport et al., 2003; Dinan et al., 2004). Other authors have demonstrated that GR signalling is reduced in

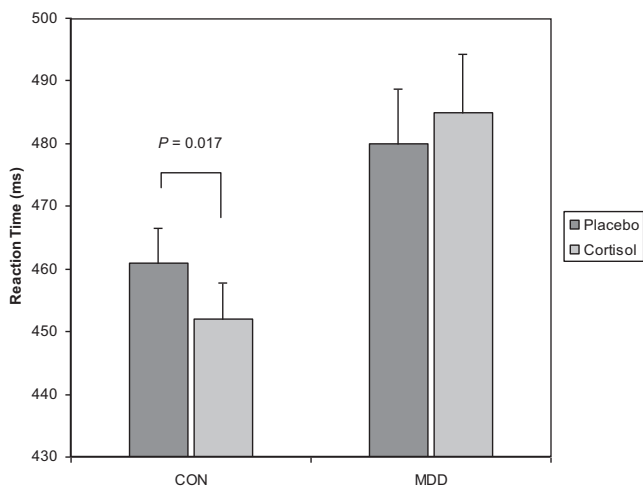


Fig. 2 Reaction times (mean, SEM) in patients with major depressive disorder (MDD) and healthy control participants (CON) after administration hydrocortisone or placebo in the go/no-go task. Taken from: Schlosser et al., in press *Psychiatry Research*.

depression, suggesting that the brain is in a state of glucocorticoid resistance (Pariante et al., 2004). As described above, GR exhibit a high density in the hippocampus (de Kloet et al., 2005), which is important for successful memory retrieval. Especially in this brain region, reduced GR mRNA has been found in MDD patients (Webster et al., 2002), which can also result in a diminished effect of glucocorticoids on memory function. Thus, the lack of an effect of acute cortisol administration on memory retrieval might be due to reduced functioning of hippocampal GR and also MR. However, the existing studies in MDD do not allow to exactly to disentangle the different effects of GR and MR on memory. We will discuss further potential interpretations and implications of these finding more detailed in Section 5.

3. Posttraumatic stress disorder

3.1. Clinical features and HPA axis alterations

Posttraumatic stress disorder (PTSD) can occur after exposure to a traumatic stressor, defined as a threat to the life of self or close others, associated with intense fear, horror, or helplessness. Traumatic experiences include childhood abuse, accident, rape, assault, war, and natural disaster. PTSD is characterized by three distinct but co-occurring symptoms: re-experiencing the trauma, avoidance and hyperarousal. Stress-induced changes in neurobiological systems are believed to be essential for PTSD symptoms, such as an enhanced sensitization to stress and enhanced physiological arousal (Heim and Nemeroff, 2009). Neuropsychological alterations are also an important feature of the clinical presentation of PTSD. Several studies revealed problems with learning and memory, including deficits in verbal declarative memory functions and attention (Golier and Yehuda, 2002) as well as reduced autobiographical memory specificity and overgeneralized memory (Buckley et al.,

2000). Of note, autobiographical memory is implicated in PTSD, e.g. in terms of intrusive memories.

Cortisol findings in PTSD suggest reduced rather than enhanced basal cortisol concentrations (Yehuda, 2002). However, these results are not consistent across all studies, and there are several potentially influencing factors, such as differences in trauma type, symptom patterns, gender, comorbidity with other mental disorders as well as genetic factors (Meewisse et al., 2007). Additionally, there is evidence that comorbid depression might play an important role in HPA axis alteration in PTSD. In this context it has been shown that PTSD patients with co-morbid MDD had a significantly lower ACTH response compared to patients without co-morbid MDD in the combined DEX/CRF test (de Kloet et al., 2008).

Interestingly, it has been found that lower cortisol measured shortly after the occurrence of a trauma was associated with the development of PTSD, suggesting that low cortisol concentrations might be a pre-existing risk factor that might lead to a maladaptive stress response (Yehuda, 2002). Beyond this hypocortisolism, an enhanced suppression after a low dose (0.5 mg) of dexamethasone has been reported (Yehuda, 2002). This has been interpreted in the context of increased negative feedback regulation of the HPA axis due to increased GR binding. Furthermore, there is evidence for enhanced central activity of hypothalamic CRF in PTSD (Heim and Nemeroff, 2009), which is supported by a blunted ACTH response to exogenous CRF, possibly due to down-regulation of pituitary CRF receptors (Heim and Nemeroff, 2009). Thus, the proposed CRF overdrive in PTSD in concert with altered function of the GR is still under discussion in PTSD.

3.2. Cortisol and cognition in PTSD

Studies that have investigated the effects of GC treatment on learning and memory in PTSD have yielded inconclusive results. One study reported a stronger negative effect of cortisol on declarative memory in PTSD compared to controls. Furthermore, in contrast to the control group, patients showed impairments in working memory after pharmacological treatment (Grossman et al., 2006). In older PTSD patients, further evidence for a more pronounced effect of cortisol was obtained, but this time enhanced working memory performance after injection of cortisol was observed (Yehuda et al., 2007a,b). Contrary, another study reported blunted effects of dexamethasone on declarative memory in PTSD (Bremner et al., 2004a,b). However, in this experiment not only the pharmacological agent but also the treatment regime differed from the other studies, i.e. dexamethasone was given for two days before memory testing. However, none of these studies focused specifically on memory retrieval, but instead administered cortisol before memory encoding and thus are unable to separate the effects of cortisol on acquisition, consolidation and retrieval. This might be one reason for the conflicting results. Another study reported that cortisol led to an impaired hippocampal-dependent trace eye-blink conditioning, a simple form of associative learning, in PTSD patients but not in healthy control participants (Vythilingam et al., 2006). Most of these findings are in line with the hypothesis

of an enhanced GR sensitivity in PTSD patients, which results in an exaggerated effect of GCs on neuropsychological functioning (Rohleder et al., 2009).

In one of our own studies, we compared PTSD patients and healthy controls with respect to the effects of cortisol on declarative memory retrieval using again a word list task and an autobiographic memory test. In both tests, opposing effects of cortisol on memory were observed when comparing patients with controls (Wingenfeld et al., 2012). In controls, cortisol had, as expected, impairing effects on memory retrieval, while in PTSD patients enhancing effects of cortisol administration on memory retrieval occurred, i.e. a higher percentage of words retrieved (see Fig. 3A) and more specific autobiographic memory retrieval (see Fig. 3B) after cortisol compared to placebo. In the placebo condition, memory performance was worse in PTSD patients compared to the controls group, which is in line with the literature (Golier and Yehuda, 2002). After cortisol administration these differences diminished. Thus, cortisol administration seems to normalize memory retrieval in PTSD in the used memory tasks. In addition, we could show that cortisol led to faster memory retrieval compared to placebo in the autobiographic memory test. This effect was seen in response to positive and to neutral cue-words, but not in response to negative cue-words (Wingenfeld et al., 2013a,b).

As the effects of GCs on memory are mostly discussed in the context of GR functioning, our results of enhancing rather than impairing effects of cortisol administration on hippocampal based memory retrieval in PTSD suggest an enhanced GR reactivity to exogenous cortisol in these patients. This interpretation is supported by a neuroimaging study with veterans suffering from PTSD. Here, administration of cortisol resulted in enhanced activity of the hippocampus, which was not detected in control veterans without PTSD (Yehuda et al., 2010a). However, the role of GR function in PTSD is still matter of debate. While there is evidence derived for an enhanced GR sensitivity in PTSD from a study which measured dexamethasone inhibition of lipopolysaccharide induced interleukin-6 and tumor necrosis factor-alpha production (Rohleder et al., 2004), other studies could not confirm these results (Pace et al., 2011).

The findings of enhanced memory after cortisol treatment in PTSD patients share similarities with an interesting observation in rodents. Rats which have been exposed to stress early in life display impaired neural plasticity (long term potentiation; LTP) in adulthood. Corticosterone treatment enhanced LTP in these animals, while impairing it in the non-stressed control animals (Champagne et al., 2008). Thus, early adversity appears to influence the response of the hippocampus to glucocorticoids in adulthood, most likely via epigenetic mechanisms. Of note, the majority of the patients in our study reported PTSD due to early trauma.

Alternatively, memory improvement after cortisol administration has been interpreted in the context of inhibition of central CRF release through cortisol administration (Yehuda et al., 2007a,b). In PTSD, a hypersecretion of CRF has been discussed (Yehuda, 2002; Heim and Nemeroff, 2009). Again, in addition to GR, mineralocorticoid receptors (MR) may play an important role in these processes (Joels et al., 2008). A more detailed discussion will be performed in Section 5.

4. Borderline personality disorder

4.1. Clinical features and HPA axis alterations

Borderline personality disorder (BPD) is characterized by intense and rapidly changing mood states as well as by impulsivity, self-injurious behaviours, fear of abandonment, unstable relationships and unstable self-image. Patients with BPD often suffer from comorbid axis I disorders, with mood disorders and anxiety disorders being the most prominent. As early adverse life experiences are highly prevalent in BPD, exposure to childhood trauma is recognized as a major antecedent for BPD (Wingenfeld et al., 2010).

As cognitive disturbances are seen in many mental disorders, several studies aimed to characterize neuropsychological functioning of BPD patients. Although the results of many of these studies suggested a significant impairment concerning episodic memory functioning (Ruocco, 2005), other studies were unable to detect such deficits (Beblo et al., 2006). Interestingly, the pattern of results changed when emotional valence was additionally considered in more sophisticated experimental designs. The outcomes of many of these studies showed deficits among BPD patients regarding the control and inhibition of emotional interference (Domes et al., 2006; Hurlmann et al., 2007). Accordingly, it has been suggested that verbal memory functions in BPD is not impaired in general, but that control and inhibition of interference with emotionally significant material might be disturbed (Mensebach et al., 2009). Furthermore, comorbid disorders, such as PTSD, seem to play an important role in explaining the cognitive problems, e.g. an attentional bias found in these patients (Wingenfeld et al., 2009).

Most studies that investigated the HPA axis in BPD revealed higher basal cortisol concentrations in concert with a reduced feedback sensitivity, but also contrary results have been reported (Wingenfeld et al., 2010). Comorbid disorders, such as MDD and PTSD, may play an important role in terms of HPA alterations in BPD and may contribute to these inconsistencies. Furthermore, an exaggerated ACTH and cortisol response in the combined DEX/CRF test has been found, but only among those who reported childhood abuse (Rinne et al., 2002). Again comorbid disorders, especially PTSD, seem to have an important influence on endocrine reactions (Wingenfeld et al., 2010). One of our own studies suggested similarities between BPD patients and MDD patients with respect to cortisol release (Carvalho Fernando et al., 2012). Reviewing these results, we hypothesized that there are at least two subgroups of BPD patients with different endocrine patterns: one predominantly characterized by trauma-associated symptoms with unaltered to enhanced feedback sensitivity and normal to reduced cortisol release, and another subgroup with mood disturbances as core symptoms and HPA axis dysfunction in form of enhanced cortisol release and reduced feedback sensitivity (Wingenfeld et al., 2010) (see Fig. 4). Furthermore, early trauma seems to play an important role in this context (Rinne et al., 2002).

4.2. Cortisol and cognition in BPD

Compared to other mental disorders, the association between memory dysfunctions and HPA axis dysregulations

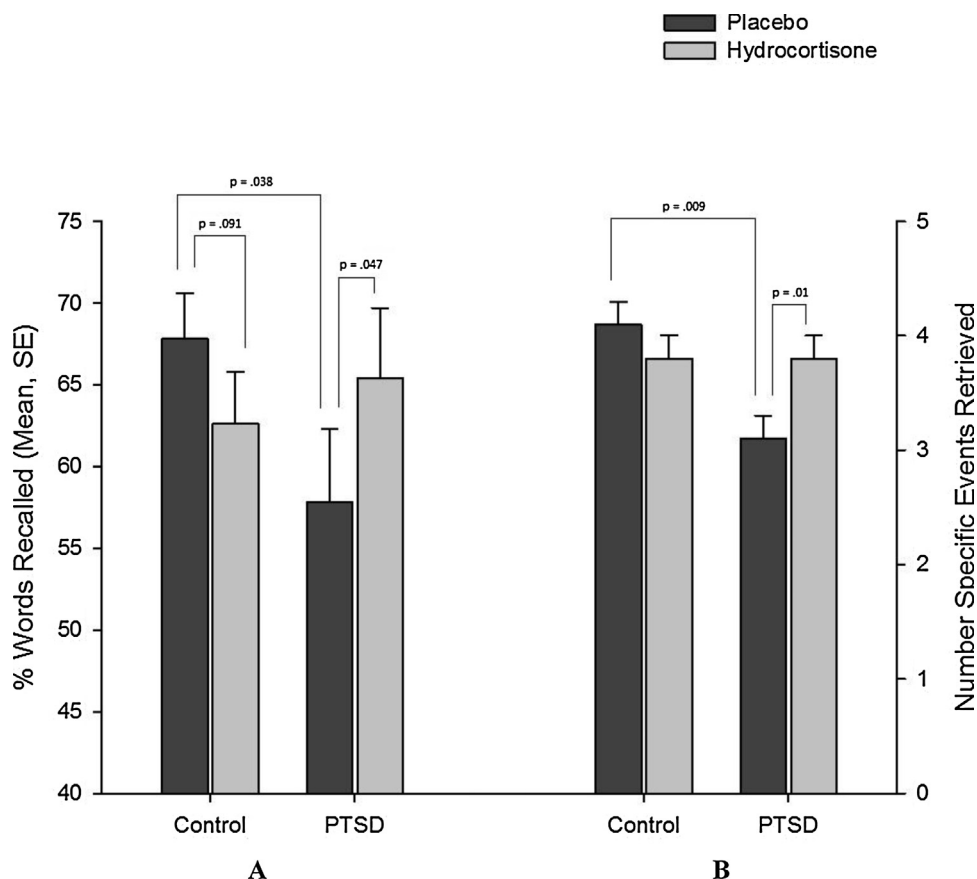


Fig. 3 The effects of 10 mg hydrocortisone on (A) percentage of words retrieved in the word list paradigm in relation to the learning list on the previous day (mean [SE]) and (B) on autobiographic memory retrieval (number of specific events retrieved; mean [SE]) in patients with PTSD in comparison to sex and age-matched healthy controls. Adapted from: [Wingenfeld et al., 2012](#) *Psychoneuroendocrinology* 37, 1048–1056

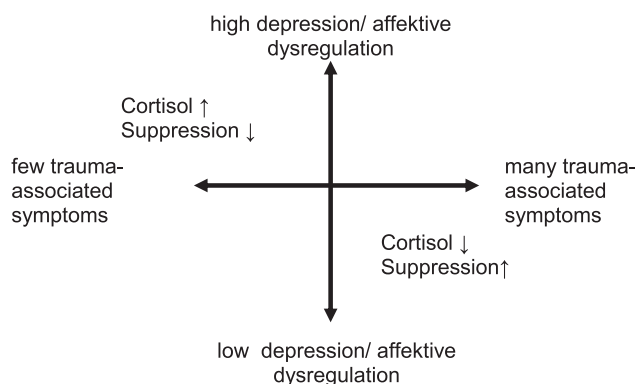


Fig. 4 The association between HPA axis dysregulation (basal cortisol concentrations and cortisol suppression (feedback sensitivity) after Dexamethasone application) and core psychopathology in BPD: Two potential dimensions. Taken from: [Wingenfeld et al., 2010](#) *Psychoneuroendocrinology* 35, 154–170.

have attracted little scientific attention in BPD. For a long time, there was no study published that investigated the effects of cortisol administration on cognition in BPD. In a placebo-controlled crossover study, we investigated a large

sample of 71 women with BPD and 40 healthy controls and compared memory retrieval after administration of either placebo or cortisol ([Wingenfeld et al., 2013a,b](#)). Again, the word list learning task, an autobiographical memory test as well as our working memory test were applied. Similar to our findings in PTSD patients, opposing effects of cortisol on memory were observed when comparing patients with controls. In controls, cortisol had impairing effects on memory retrieval, while in BPD patients cortisol had enhancing effects on memory retrieval of words, on autobiographical memory, and on working memory. These effects were most pronounced for specificity of autobiographical memory retrieval. Concerning the word list learning task, we also analysed whether comorbid PTSD and MDD influenced the results: patients with BPD alone as well as with comorbid PTSD showed the effect of better memory retrieval performance in response to cortisol. However, in the subgroup of BPD patients with comorbid MDD the effects of cortisol on memory were absent (see [Fig. 5](#)) ([Wingenfeld et al., 2013a,b](#)). The latter result suggests that these patients differ from other BPD patients in terms of their sensitivity to GCs, but show a similar pattern as seen in patients with MDD alone (described in Section 2.2). Concerning response inhibition in an emotional go/no-go task, no differences between healthy control participants and BPD patients were found:

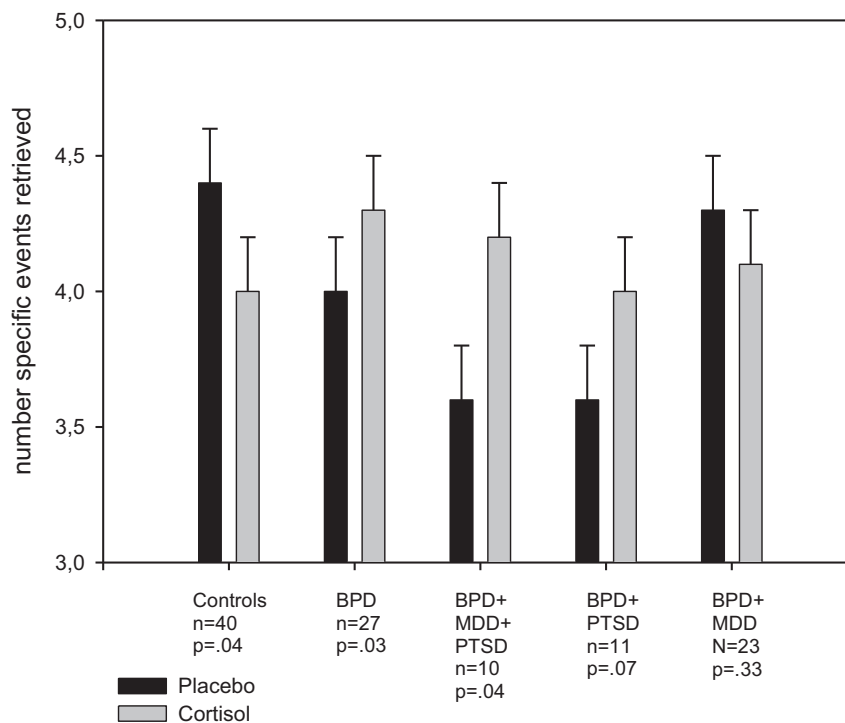


Fig. 5 Memory specificity after placebo and hydrocortisone: Analyses of BPD subgroups with different comorbid disorders (n = sample size per subgroup, p = post-hoc t -test placebo vs. cortisol). Taken from: [Wingenfeld et al., 2013a,b](#) *Psychological Medicine* 43, 495–505.

both showed decreased reaction times to target stimuli in response to acute cortisol elevations ([Carvalho Fernando et al., 2013](#)).

The positive effects of cortisol on memory retrieval in BPD share similarities with our findings in patients with PTSD. Thus, one might also speculate about beneficial effects of cortisol on hippocampal (and prefrontal) mediated memory processes in patients with BPD. As BPD patients have a high prevalence of adverse or traumatic experiences early in life, the study of [Champagne et al. \(2008\)](#) might help to understand our results. As mentioned above, in this study corticosterone treatment enhanced long-term potentiation (LTP) in adult animals which have been exposed to early life stress, while it impaired LTP in the non-stressed control animals ([Champagne et al., 2008](#)).

In a very recent study, we aimed to take a closer look at role of the MR in the context of social cognition in patients with BPD ([Wingenfeld et al., 2014](#)). Of note, deficits in social cognition are discussed for several mental disorders, including BPD ([Roepke et al., 2012](#)). A phenomenon closely related to social cognition is empathy, which consists of at least two components: The first is a cognitive component, which captures the capacity to infer others' mental states and is also referred to as perspective taking, mentalizing, or theory of mind. Second, empathy also comprises an affective component, i.e., an emotional response to another person's emotional state ([Roepke et al., 2012](#)). In a placebo-controlled study, we randomized 38 female BPD patients without psychotropic medication and 35 healthy women to either placebo or 0.4 mg fludrocortisone, an MR agonist. Subsequently, all participants underwent the Multifaceted Empathy Test (MET) which measures cognitive and

emotional empathy ([Wingenfeld et al., 2014](#)). We found that fludrocortisone enhanced emotional empathy across groups while cognitive empathy was not affected, suggesting a positive effect of MR stimulation on social cognition ([Wingenfeld et al., 2014](#)). This fits very well with animal data showing that MR are particularly involved in the appraisal of novel situations and in modulating stress-associated emotional reactions ([de Kloet, 2013](#); [Kruk et al., 2013](#)). On a first view one might wonder why fludrocortisone affects cognition due to the fact that it has been suggested that intracellular MR are mostly occupied under basal condition. Interestingly, there are studies which show that the proportion of MR that were occupied by low basal corticosterone levels was overestimated ([Kalman and Spencer, 2002](#)). Moreover membrane bound MRs appear to have a lower affinity for cortisol and thus might mediate some of the rapid behavioural effects of cortisol or MR agonist administration reported in this manuscript. Whether fludrocortisone might play a therapeutic role in psychotherapeutic processes, remains to be elucidated.

5. Conclusions and potential implications

In a series of studies, we investigated the effects cortisol on declarative memory retrieval, autobiographic memory and working memory, in mental disorders such as MDD, PTSD and BPD. In MDD and BPD, we also investigated effects on response inhibition. Healthy control participants showed impaired memory retrieval after cortisol administration compared to placebo, as expected. Response inhibition was facilitated through cortisol. These results replicate the well

established finding of corticoids on cognition. As there are several excellent reviews on this topic, we will not further discuss the effects in healthy participants but focus on the effects of cortisol on memory in mental disorders. Additionally, we like to mention that our recent research further emphasizes the importance of MR in the context of social cognition as we could show improving effects of MR stimulation on emotional empathy.

While in patients with MDD cortisol administration failed to effect memory retrieval in all investigated cognitive domains, patients with PTSD and BPD showed enhanced rather than impaired memory retrieval after cortisol administration. Overall, this indicates an altered sensitivity to stress hormones in these disorders which differs between MDD and PTSD and BPD, respectively. Patients with PTSD and BPD show comparable responses to cortisol administration in terms of effects on memory retrieval. Interestingly, in BPD patients who also suffer from current MDD cortisol administration failed to effect memory retrieval as seen in MDD patients before. Of note, comorbid psychiatric disorders have been found to be differentially associated with HPA axis alterations in BPD (Wingenfeld et al., 2010). In a former review, we hypothesized that there might be two subgroups of BPD patients with different endocrine patterns (Wingenfeld et al., 2010). Our current results may further contribute to our hypothesized model: In addition to unaltered to enhanced feedback sensitivity and normal to reduced cortisol release the subgroup of BPD patients without comorbid major depression but (in part) with comorbid PTSD symptoms seems to be characterized by an enhanced reactivity to exogenous cortisol in terms of memory retrieval. The other subgroup, i.e. BPD with comorbid depression characterized by enhanced cortisol release in concert reduced feedback sensitivity show a lack of effects of cortisol on memory. Future studies need to investigate the longitudinal course of HPA axis regulation, i.e. whether the missing effect of cortisol on memory diminishes if the depressive episode remits. Interestingly, for PTSD patients the importance of comorbid depression has been also demonstrated (de Kloet et al., 2008). However, in our study we could not see differences between PTSD patients with and without current MDD with respect to the effects of cortisol on memory retrieval (Wingenfeld et al., 2012).

The effects of GCs on memory are mostly discussed in the context of corticoid receptor functioning. Thus, for interpretation of the data we will focus on studies on GR (and MR) alterations in the investigated disorders. Furthermore, neuroimaging studies may help to understand the data since they can pinpoint to the brain regions involved.

5.1. Altered GR/MR function

In sum, the mental disorders discussed here appear to be characterized by distinct patterns of HPA axis dysregulation, with some similarities at central levels of the HPA axis, i.e. exaggerated CRF activation, but distinctions at the periphery. While MDD and BPD seem to be characterized by higher cortisol secretion accompanied by reduced feedback sensitivity, there is some evidence for lower cortisol concentrations and enhanced feedback sensitivity in PTSD. Altered feedback sensitivity is mostly discussed in terms of altered GR or MR receptor functioning. Because most of the effects

associated with GCs – especially those that are related to the CNS – have been attributed to GR, we will first focus on this particular receptor type.

There is compelling evidence for altered GR function, i.e. a reduced sensitivity, in patients with MDD. Corresponding studies include not only DEX and DEX/CRF tests but measurements of GR mRNA, GR gene polymorphisms and methylation of the GR gene promoter (Webster et al., 2002; Binder et al., 2004; McGowan et al., 2009; Otte et al., 2009b). The missing impairing effects of cortisol on memory in MDD patients fit well to the hypothesis of impaired GR functioning in MDD.

Contrary, in PTSD there is evidence for increased GR binding (Rohleder et al., 2004; Yehuda, 2009), but there are also contradictory findings (Pace et al., 2011). Thus, altered function of the GR is still under discussion in PTSD. However, most studies, including our own, which investigated the effects of corticoids on memory in PTSD, suggest an enhanced sensitivity for the effects of cortisol (Yehuda et al., 2007a,b; Yehuda et al., 2010a; Wingenfeld et al., 2012). Additionally, there is evidence that cortisol treatment may reduce involuntary retrieval of traumatic memory, i.e. flashbacks (Aerni et al., 2004). Furthermore, beneficial effects of cortisol have been shown in the context of prevention of PTSD symptoms after acute trauma experiences (Schelling et al., 2001; Schelling et al., 2004). In sum, there is growing evidence for – in part – beneficial effects of cortisol in PTSD, i.e. normalization of controlled and voluntary memory retrieval and reduction of uncontrolled involuntary memory retrieval. Of note, PTSD is characterized by overwhelming, intrusive memories which are very vivid and often detailed in concert with psychogenic amnesia, i.e. forgetting of important aspects of the trauma, which has been discussed as ‘memory paradox’ paradox in PTSD (Yehuda et al., 2010b).

In BPD, only very few studies investigated the GR. One study for example reported a significant positive correlation between methylation status of the promoter region of the glucocorticoid receptor gene clinical severity (Martin-Blanco et al., 2014). Another study showed that in a sample of bulimic patients comorbid BPD was associated with significantly more methylation (Steiger et al., 2013). Future research is warranted here.

It has been suggested that GR mediate the impairing effects of cortisol, while MR along with a moderate GR occupation might facilitate hippocampal function (Joels and Krugers, 2007; Ferguson and Sapolsky, 2008). Up to now, studies investigating the role of MR function on memory in humans are rare (Otte et al., 2007; Cornelisse et al., 2011; Rimmele et al., 2013; Wingenfeld et al., 2014), but emphasize the importance of the MR in terms of memory and cognition especially in light of the recently characterized membrane bound MR.

In MDD, there is growing evidence suggesting that MR dysfunction might also play a role (de Kloet et al., 2005; Otte et al., 2009a; Rohleder et al., 2009). In light of the MR/GR balance model of depression (de Kloet, 2013), combined investigations of both receptors are now required. Only few studies investigated the MR in PTSD patients (Kellner et al., 2002; Otte et al., 2006), suggesting unaltered MR function in these patients. In BPD, such studies are completely missing. For a better understanding of endocrine and cognitive disturbances as well as their interactions, the

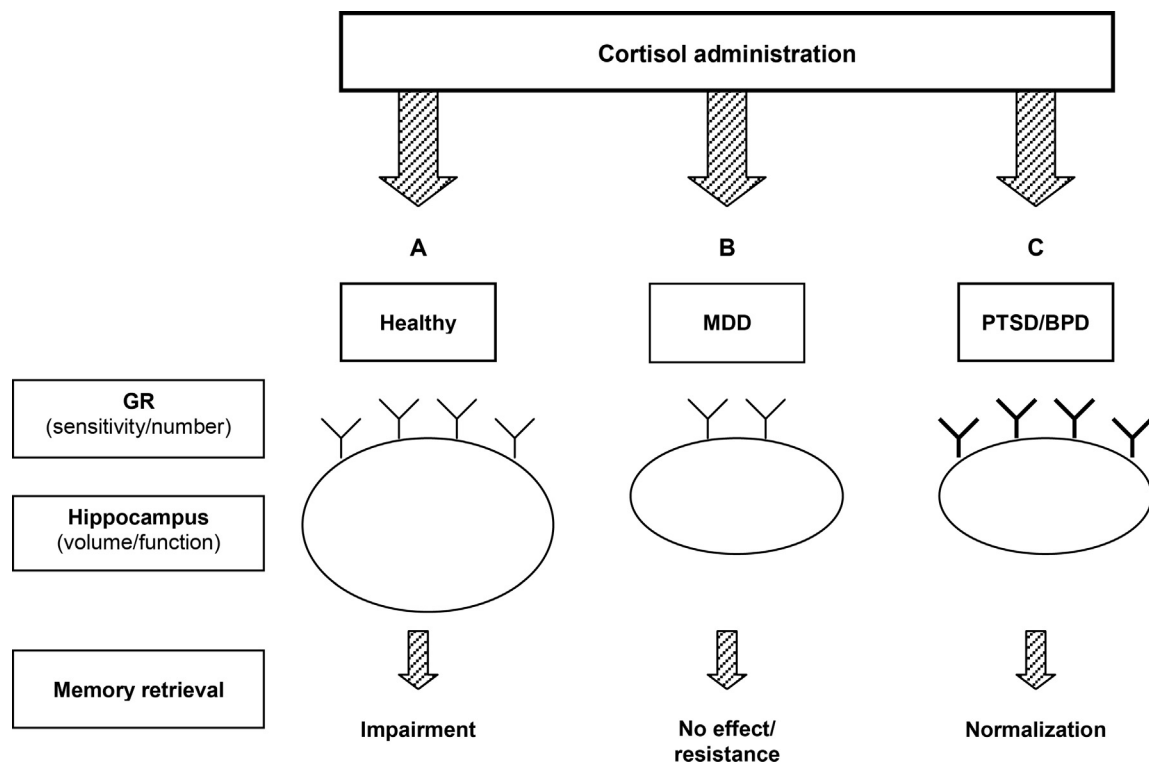


Fig. 6 Effects of cortisol administration on memory retrieval in healthy humans, patients with MDD and patients with PTSD/BPD. A hypothetical model: (A) in healthy participants GC leads to impairments in memory retrieval; (B) in patients with MDD, which are characterized by reduced hippocampal size and function in concert with GR resistance, no effects of GCs on memory are seen; (C) patients with PTSD/BPD are also characterized by reduced hippocampal size and function but might have an enhanced GR sensitivity leading to a normalization of memory retrieval performance after GC administration. *Abbreviations:* MDD = major depressive disorder, PTSD = posttraumatic stress disorder, BPD = borderline personality disorder, GC = glucocorticoids, GR = glucocorticoid receptor.

interplay between both receptor types in terms of impairing and facilitating memory processes should be investigated comprehensively.

5.2. Imaging studies of glucocorticoid effects

Many studies used imaging techniques to evaluate structural changes in the brain of patients with mental disorders. Due to the high density of GC receptors in the hippocampus, this brain structure is thought to be a sensitive region for the effects of chronic stress or chronically elevated GCs (de Kloet et al., 2005).

In MDD, hippocampal volume reduction is a prominent finding, but several factors as childhood trauma and illness duration seem to be associated with a smaller hippocampal size as well (Heim and Binder, 2012). A reduced hippocampal size has been also reported for PTSD patients (Karl et al., 2006). This finding was formerly interpreted as a result of enhanced cortisol release in response to the trauma, but it might also be a pre-existent risk factor (Gilbertson et al., 2002). In BPD, there are also several structural imaging studies focussing on the hippocampus, suggesting a hippocampal volume reduction (Wingenfeld et al., 2010). Regarding hippocampal volume reduction, there are impressive similarities between MDD, PTSD and BPD patients. One might suggest that disturbances in the hippocampal integrity might be a non-specific risk factor for the

development of psychiatric disorders, possibly reflecting early adversity.

Imaging studies with healthy participants showed that cortisol administration leads to a reduced activity in the hippocampus during resting state conditions (Lovallo et al., 2010) and while memory retrieval (de Quervain et al., 2003; Oei et al., 2007; Weerda et al., 2010). Furthermore, the reduced brain activation after cortisol administration was associated with cortisol induced memory retrieval impairment (de Quervain et al., 2003). In psychiatric patients, comparable studies are missing. There is only one single study in PTSD patients that investigated the response to cortisol administration. This study reports a different pattern as the described above: Interestingly, PTSD patients had not a reduced, but an enhanced hippocampal activity after cortisol intake (Yehuda et al., 2010a). A recent study reported that in Dutch soldiers the number of (peripheral) GR before deployment predicts an increase in amygdala activity to emotional faces after severe stress as the deployment to Afghanistan (Geuze et al., 2012).

Up to now, the effects of cortisol administration on brain activity in patients with MDD and BPD have not been investigated. However, further studies using functional imaging may help to understand the reported results.

The neural underpinnings of exogenous (and endogenous) cortisol and its effects on cognitive function should be investigated in concert with GR measurements.

5.3. Summary and hypothesized model

In PTSD, most HPA axis findings, i.e. basal cortisol concentration, feedback sensitivity and GR sensitivity, are opposing to those found in MDD and BPD. Of note, HPA axis alterations in BPD are strongly influenced by comorbid disorders as MDD. On a central level of the HPA axis, there is evidence for exaggerated CRF activity for all of these disorders. Concerning the effects of GCs on memory, MDD patients (including BPD patients with comorbid MDD) show a resistance to the effects of cortisol, while patients with PTSD and BPD (without comorbid MDD) seem to profit from cortisol administration in terms of memory retrieval.

Thus, one might hypothesize that in MDD impaired hippocampal integrity in concert with impaired GR function results in a GC resistance, and, thus, in lacking effects of cortisol on cognition (see also chapter 2). PTSD and BPD patients also show hippocampal dysfunctions but a more pronounced GR sensitivity, resulting in a state where cortisol effects turn beneficial. These hypotheses are visualized in Fig. 6.

The underlying mechanisms are still a matter of debate: (1) GC administration might enhance hippocampal activity directly, as suggested by a study in PTSD patients (Yehuda et al., 2010a). Furthermore, there is evidence for improved hippocampal LTP after GC elevation in animals stressed early in life which might reflect (2) an enhanced hippocampal plasticity (Champagne et al., 2008) and which might also be associated with the observed memory improvement. (3) One might further speculate that the beneficial effects of GCs in PTSD and BPD patients are related to a cortisol induced shift towards non-hippocampal based memory retrieval processes which might rescue performance, at least in part. Similar compensatory shifts between multiple memory systems have been observed in rodents and humans, e.g. a shift from cognitive to habit strategies (de Kloet, 2010; Schwabe and Wolf, 2012). Furthermore, it is known from former research, that the context in which GC increase takes place influences its effects, resulting in beneficial or negative outcome (de Kloet, 2010). The underpinning mechanisms of this “glucocorticoid paradox” (de Kloet, 2010) needs further scrutiny. A more detailed knowledge on the interplay between GR and MR on cognitive processes under stress and, thus, alterations in GR/MR balance in mental disorders will be helpful. Our study using MR stimulation suggests unaltered MR function in patients with BPD as positive effects of fludrocortisone on empathy were seen in patients and healthy participants. In the context of PTSD and BPD, future studies should investigate the underlying mechanism of the beneficial effects of GCs on memory retrieval, e.g. by combining imaging and endocrine methods.

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Conflict of interest statement

There were no conflicts of interest, financial or otherwise, to declare.

Contributors

Katja Wingenfeld: Was PI of the presented studies and wrote the manuscript.

Oliver T. Wolf: Contributed to the designs of the studies and the discussion of the findings. Revised the first draft of the manuscript and approved the final version.

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