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# Mineralocorticoid receptor function and cognition in health and disease

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ABSTRACT

The steroid hormone cortisol is released in response to stress and exerts its effects in the brain via two different receptors: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). This review - dedicated to Dirk Hellhammer - focusses on the role of MR on cognitive and emotional function in healthy individuals and in stress-associated disorders such as major depressive disorder (MDD) or borderline personality disorder (BPD).

Animal data and studies from healthy individuals converge such that MR play an important role in the appraisal of new situations and the following response selection. Decision-making and empathy are important determinants of this response selection and both are affected by MR function. Furthermore, MR are crucially involved in visuospatial navigation and memory in young and elderly healthy individuals whereas the exact physiological role of MR in verbal learning and verbal memory needs to be further characterized.

In contrast to studies in healthy participants, age played a moderating role on the effects of MR stimulation on cognition in depressed patients. In young depressed patients, MR stimulation exerted beneficial effects on verbal memory and executive function, whereas in elderly depressed patients MR stimulation led to impaired verbal learning and visuospatial memory. Similar to healthy controls, BPD patients showed enhanced emotional empathy but not cognitive empathy after MR stimulation. Accordingly, this make MR an interesting target for potential pharmacological augmentation of psychotherapy in BPD.

Given the important role MR play in cognitive and emotional function in health and disease, further studies should examine whether MR modulation can alleviate cognitive and emotional problems in patients with stress-associated disorders.

## 1. Introduction

Stress, such as early life adversity or traumatic life events, is a risk factor for many psychiatric disorders including major depressive disorder (MDD) (Otte et al., 2016), posttraumatic stress disorder (PTSD), or borderline personality disorder (BPD) (Wingenfeld and Wolf, 2015). All of these disorders are characterized by alterations in cognitive and emotional function and by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis leading to altered secretion of the stress hormone cortisol (Wingenfeld and Wolf, 2015). Importantly, cortisol affects multiple brain structures associated with cognitive and emotional function (de Kloet et al., 2018; Joels et al., 2013). Therefore, alterations in cortisol secretion likely contribute to impaired cognitive and emotional function in these disorders. In turn, intervening within the HPA system might a promising approach to alleviate the cognitive and emotional problems to some extent (Wingenfeld and Wolf, 2015).

In addition to its circadian secretion, cortisol is released in response to stress. Cortisol exerts its effects in the brain via two different nuclear receptors that act as transcription factors: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). GR are ubiquitously expressed in neurons and glia cells with highest expression in stress-responsive brain structures such as the hypothalamus, hippocampus, amygdala, and ascending aminergic neurons (de Kloet, 2013). GR have a low affinity for cortisol and become only gradually occupied during the circadian peak or during higher cortisol concentrations after stress. In contrast, MR have an about 10fold higher affinity for cortisol and are largely but not fully occupied already under basal cortisol concentrations (de Kloet et al., 2018; Kalman and Spencer, 2002; Pace and Spencer, 2005). MR are abundantly expressed in limbic brain structures such as the hippocampus, amygdala, and prefrontal cortex and exert a basal inhibitory tone on cortisol secretion (de Kloet et al., 2016).

In addition to nuclear GR and MR that mediate slow genomic effects of cortisol, animal and human studies have additionally revealed the existence of membrane bound GR and MR mediating rapid non-

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genomic effects (Henckens et al., 2011; Joels et al., 2013; van Ast et al., 2013). Because cortisol exerts many of its effects on cognition and emotion within the first hour of administration, these early effects cannot be explained by late genomic but only by early non-genomic effects (Joels et al., 2012). It is not known whether different pharmacological compounds are specific for membrane or nuclear receptors. However, it is known that membrane MR have an about 10fold lower affinity for cortisol compared to nuclear MR. Therefore, membrane MR will only increasingly be occupied during higher cortisol concentrations or after pharmacological stimulation. It is plausible that MR serve additional functions apart from basal inhibition of HPA activity. Indeed, this has lead to the hypothesis that particularly the MR is of great importance in the initial phase of the stress response (Joels et al., 2012).

Supporting this hypothesis, animal studies have shown that MR are particularly involved in the appraisal of novel (emotional) situations and in early selection of response strategies (de Kloet, 2013; Hamstra et al., 2015; Ter Horst et al., 2014). In this context, MR are important in modulating stress-associated emotional arousal and adaptive behaviors (Brinks et al., 2007; Schwabe et al., 2010) apparently in part based on the genetic background (Wirz et al., 2017). Of note, in a stressful situation human individuals need to decide immediately how to act and emotional appraisal and reaction is often essential in the context of perceived danger and anxiety. As indicated above, MR are expressed in high density in limbic brain areas, which are involved in the processing of emotional information (Groeneweg et al., 2012; Joels et al., 2011). Therefore, it is biologically plausible that MR are crucially involved in emotional and cognitive function in stressful situations and that they might be altered in stress-associated disorders.

In addition to appraisal and early response selection, animal studies have additionally shown a crucial role for MR in memory function (Joels et al., 2008). Early pioneering studies by Oitzl and coworkers provided clear evidence for a role of MR on spatial memory (Oitzl and de Kloet, 1992; Oitzl et al., 1994). Blockade of MR impairs spatial memory and working memory (Berger et al., 2006). In contrast, overexpression of MR has been consistently associated with improved memory in animals (Ferguson and Sapolsky, 2008; Harris et al., 2013; Kanatsou et al., 2017; Lai et al., 2007; Rozeboom et al., 2007).

So far, most studies have focused on GR function when appraising glucocorticoid effects on the brain, on cognition, and on psychopathology and there are several excellent reviews on GR function available (Anacker et al., 2011; Gray et al., 2017). This review aims to more specifically provide an overview of human studies that have examined the role of MR function on cognitive and emotional function in healthy individuals and in patients with stress-associated disorders.

## 2. Mineralocorticoid receptor function and cognition in healthy individuals

It is well established that in healthy individuals memory consolidation is enhanced, whereas memory retrieval is impaired by increased cortisol concentrations (Wingenfeld and Wolf, 2014; Wolf, 2009). Most of these experimental studies used psychosocial stress exposure or cortisol administration, which leads to a stimulation of both receptor types, the GR and the MR. However, during the last ten years more and more studies examined the specific role of the MR in memory function and other cognitive domains. Most of these investigations used a single administration of spironolactone to block MR function or fludrocortisone to stimulate MR function. Some of these studies combined MR blockade with psychosocial stress induction to identify the specific role of the MR in the context of stress-induced cognitive alterations.

### 2.1. Effects of MR blockade on cognition

It has been shown that pharmacological blockade of the MR compared to placebo led to impaired memory function in humans (Otte et al., 2007; Rimmele et al., 2013; Young et al., 2016). For instance, after administration of the MR antagonist spironolactone one study found impaired free retrieval of both texts and pictures, which had been learned three days earlier (Rimmele et al., 2013). This effect was most pronounced for emotional stimuli. When looking at autobiographical memory retrieval, MR blockade impaired retrieval relative to placebo, as indicated by changes in the percent of specific memories recalled (Young et al., 2016). Due to the high density of MRs in the hippocampus, particularly spatial memory has been suggested to be sensitive to MR modulation. Indeed, MR blockade impaired delayed retrieval of visuospatial memory, measured with the Rey-Taylor complex figure test (Otte et al., 2007). Taken together, these results support the hypothesis, that MR play an important role in (hippocampal-based) memory retrieval.

However, when investigating verbal learning performance, two studies did not reveal an effect of MR blockade on the learning curve in a word list learning paradigm (Otte et al., 2007; Young et al., 2016). This is in line with another study, which did not find an effect of spironolocatone on verbal learning and working memory (Cornelisse et al., 2011). Apart from learning and memory, many other cognitive domains are influenced by stress and stress hormones. The effects of MR blockade on selective attention, measured with the d2 test of attention, has been investigated in two independent studies, which both showed an impairment after spironolcatone compared to placebo (Cornelisse et al., 2011; Otte et al., 2007). In contrast, there was no effect on psychomotor speed and cognitive set shifting assessed with the trail making test (TMT A & B) (Otte et al., 2007).

In sum, MR blockade seems to impair some cognitive domains such as selective attention and memory. Concerning memory retrieval, especially visuospatial and autobiographic memory seem to be affected, while the effects on verbal memory retrieval are more ambiguous (see also Table 1). However, in those studies which did not find an effect of MR blockade on memory retrieval, the time between learning and memory retrival was relatively short. Therefore, encoding, consolidation and memory retrieval were not temporally separated. All memory processes were affected by the pharmacological treatment making it difficult to disentangle the effects of spironolactone on different memory phases (Otte et al., 2007; Young et al., 2016). In any event, verbal learning as expressed in a learning curve in a word list learning test seems to be unaffected by MR blockade.

When appraising the findings of cognitive function after MR blockade, it is important to keep in mind that cortisol concentrations rise after MR blockade as has been shown consistently (Cornelisse et al., 2011; Otte et al., 2007; Rimmele et al., 2013; Young et al., 1998). GR blockade leads to elevated cortisol as well (Block et al., 2018; Rimmele et al., 2013). Thus, blockade of MR shifts the MR/GR balance towards more GR binding and vice versa. These complex effects on the MR/GR balance likely contribute to effects of MR and GR blockade on cognition.

### 2.2. Effects of stress on cognition after MR blockade

Another approach to investigate the stress-dependent role of MR on cognition is to block MR in a first step and to provoke a cortisol response by stressing the individual afterwards. This procedure leads to high cortisol levels in parallel to blocked MR function.

Interestingly, in contrast to spironolactone treatment alone, the combination of spironolactone with psychosocial stress induction led to impaired working memory performance (Cornelisse et al., 2011). This supports the important role of MR in memory function as found in the studies above that did not use a stress-paradigm but MR blockade only. Furthermore, neither stress nor MR blockade alone affected delayed memory retrieval measured 24 h later, but in the group which received spironolactone before being stressed delayed memory retrieval was improved 24 h later (Cornelisse et al., 2011). Importantly, this assessment was not a test of memory retrieval during MR blockade but of memory consolidation during the previous days when MR were

**Table 1**
Effects of MR blockade with spironolactone on cognition in healthy individuals.

| Study (Dosage) | Encoding | Verbal memory retrieval | Visuo-spatial memory | Working memory | Autobiogra-phic memory | Selective attention | Executive function | Empathy |
|---|---|---|---|---|---|---|---|---|
| Otte et al.,2007 (3 x 300 mg) | word list: no effect | word list after 30 m in. no effect | impaired | digit-span: no effect | | d2 task: impaired | trail making test: no effect | |
| Cornelisse et al., 2011 (400 mg) | word list: no effect | word list after 24 h: no effect* | | n-back: no effect** | | d2 task: impaired | | |
| Rimmele et al., 2013 (2 x 200 mg) | | text (& pictures) 3 days after learning: impaired | | | | | | |
| Schwabe et al., 2013a, 2013b (300 mg) | | | | | | | Stress induced enhanced response inhibition abolished by MR blockade | |
| Schwabe et al., 2013a, 2013b (300 mg) | Probabilistic learning task: no effect*** | | | | | | | |
| Vogel et al., 2015 (400 mg) | Prevents stress induced enhanced of recall of delay conditioning | | | | | | | |
| Young et al., 2016 (600 mg) | word list: no effect | word list: no effect | | | impaired | | | |
| Wingenfeld et al., 2016 (300 mg) | | | | | | | | cognitive & emotional empathy: no effect |
| Vogel et al., 2017 (400 mg) | Prevents stress induced enhancement of stimulus-response learning | | | | | | | |

* when MR blockade was followed by a psychosocial stressor, i.e. high endogenous cortisol levels, delayed memory retrieval was enhanced.
** when MR blockade was followed by a psychosocial stressor, working memory was impaired (in the 2-back but not the 3-back test part).
*** when MR blockade was followed by a psychosocial stressor, reduced learning performance.

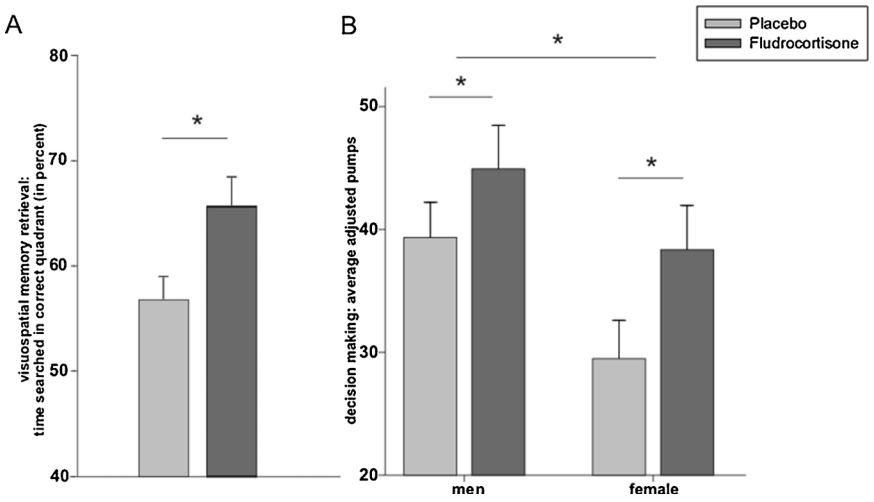


**Fig. 1.** Effects of MR stimulation with fludrocortisone on A) visuospatial memory retrieval and B) risky decision making in young healthy individuals. A) Better memory performance and B) more risky decisions after fludrocortisone compared to placebo. Fludrocortisone led to riskier decisions for both sexes, but to a greater extent for women than for men. (From: Piber et al., 2016 and Deuter et al., 2017).

blocked. As expected, the cortisol response in the combined stress/MR blockade was higher than in both other groups (stress induction or spironolactone administration alone. Thus, better memory retrieval 24 h after stress and MR blockade might be mediated through the improving effects of glucocorticoids on memory consolidation and seems to be related to GR activation.

Additionally, it has been shown that stress-induced response inhibition in a stop signal task was abolished after pretreatment with spironolactone (Schwabe et al., 2013a). In a fMRI study, MR blockade followed by a psychosocial stressor led to reduced learning performance, which was not the case after spironolactone or stress alone (Schwabe et al., 2013b). On a neuronal level, stress reduced activation of the hippocampus in favor of dorsal-striatal activations. This stress-induced shift was prevented by pretreatment with spironolactone (Schwabe et al., 2013b).

In sum, the MR seems to play a crucial role in the mediation of the well-described stress induced shift from goal-directed to habitual action (Schwabe and Wolf, 2009; Vogel et al., 2016). In terms of memory this means that during stress the flexible, cognitive hippocampus-based memory system is less dominant in favor of a more rigid or hapitual memory style, which is more striatum-associated (Schwabe and Wolf, 2013).

Additionally, it has been demonstrated that administration of spironolactone prevented stress-induced enhancement in stimulus-response learning, which was mediated by amygdala activation (Vogel et al., 2017). The same research group also used a fear conditioning paradigm, in which stress led to enhanced retrieval of delay conditioning (the unconditioned stimulus is following the conditioned stimulus (CS) during CS presentation or directly afterwards) but not trace conditioning (unconditioned stimulus presented 3 s after CS). Interestingly, this stress effect only ocurred when MR were available and not after MR blockade (Vogel et al., 2015). Notably, especially trace conditioning is strongly hippocampus-dependent. Accordingly, in the learning phase a stress-induced reduction of hippocampal activity for trace conditioning was seen. Thus, stress leads to a shift in neural activity with less hippocampal activity but increased activation of the amygdala, This process is disturbed by MR blockade.

These studies provide further evidence that MR are involved in cognitive task performance such as selective attention and in modulation of stress induced effects on cognition. Some of these results suggest that MR activation might prevent stress induced impairment in some cognitive task because stress-related impairments in working memory and learning after cortisol increase were only seen after MR blockade but not when MR function was intact (Cornelisse et al., 2011; Schwabe et al., 2013b). In contrast, stress-induced enhancement in response inhibition and stimulus-response learning – which might be interpretated as “positive” stress effects - was inhibited by MR blockade (Schwabe et al., 2013a; Vogel et al., 2017).

### 2.3. Effects of MR stimulation on cognition

So far, we have described that blockade of MR function has primarily impairing effects on several cognitive processes. This raises the question of whether increased MR activation could in turn improve cognitive function. To this end, we conducted several studies in which fludrocortisone, a MR agonist, was administered to stimulate MR activation. We found that MR stimulation led to improved visuospatial memory, improved learning - but not retrieval - of a word list, and improved working memory (Hinkelmann et al., 2015). Memory encoding and retrieval was not experimentally separated in this study. Therefore, it is not possible to disentangle the effects of MR stimulation on these memory processes. However, another study suggests that fludrocortione improves memory consolidation. In that study, fludrocortisone had no acute effect on the learning curve and the immediate retrieval of a word list, but led to better memory retrieval one day later (Groch et al., 2013).

Furthermore, we used a computer based test to measure spatial encoding and memory, the virtual Morris Water Maze, and found improved spatial memory retrieval after fludrocortisone, while spatial learning was unaffected (Piber et al., 2016) (Fig. 1 A). In contrast, we did not find an effect of MR stimulation on autobiographical memory retrieval (Fleischer et al., 2015). In sum, these studies provide first evidence that acute MR stimulation improves memory. For visuospatial memory retrieval this effect is already replicated. Notabbly, there is a strong hippocampal involvement in visuospatial memory, and the effects are likely to be explained by high MR density in this brain region.

In contrast, fludrocortisone administration did not affect performance in the trail making test B (Otte et al., 2015a) and in another task of executive function, namely mirror tracing (Groch et al., 2013). However, we demonstrated a role of the MR in selective attention: in an emotional dot probe task, fludrocortisone administration led to enhanced attentional bias towards negative faces, while there was no such effect on happy faces (Schultebraucks et al., 2016a). Furthermore, healthy individuals tended to riskier decisions when pretreated with fludrocortisone (Deuter et al., 2017) (Fig. 1 B). In sum, these findings are in line with the hypothesis that MR activation boosts the salience network and, thus, is involved in the appraisal of a novel situation, attentional vigilance to salient information, behavioral flexibility, and decision making (de Kloet, 2013; Vogel et al., 2016)

There are some important methodological aspects that need to be taken into account when interpreting fludrocortisone findings. First, fludrocortisone binds to some extent to the GR although its MR affinity

is about 150 times higher than its GR affinity (Agarwal et al., 1977). The extent of its glucocorticoid potency ranges from negligible to rather moderate depending on the source of the literature and variable being examined (Grossmann et al., 2004; Miller, 2008). In any event, remaining GR activity could contribute to the effects of fludrocortisone. Second, fludrocortisone activates not only MR in the limbic system but also aldosterone-selective MR in the nucleus tractus solitarii, which could contribute to the effects of fludrocortisone. However, after one-time administration of fludrocortisone we have never found an effect on blood pressure (Otte et al., 2015a; Wingenfeld et al., 2015), and even during a three-week treatment with fludrocortisone we have not observed an effect on sodium retention in depressed patients (Otte et al., 2010).

Of note, investigations on the role of the MR in human cognition is a relatively young field of research and there are several open questions, such as moderating effects of sex and age. As most studies investigated male samples, little is know about mentrual cycle phase or intake of oral contraceptives. This is important since spironolactone has pronounced antagonistic effects on progesterone receptors (Struthers et al., 2008). In turn, progesterone acts as a functional MR antagonist (Quinkler and Diederich, 2002). However, in one of our studies we found comparable effects of MR stimulation on visuospatial memory retrieval in women and men (Piber et al., 2016). Importantly, genetic make up seems to affect the moderating effects of sex hormones on MR-associated cognitive function because MR haplotype 2 protects against the depressiogenic effects of oral contraceptives and attenuates the effect of estradiol and progesterone fluctuations on emotional information processing (Hamstra et al., 2017, 2015).

### 2.4. Social cognition

Humans often have to perform complex social cognitive tasks while being stressed. Thus, it is of great interest to understand how stress and stress hormones influence social cognition, which can be defined as the ability to process, store, and use information about other people and social situations. Notably, several studies demonstrated that stress enhanced several aspects of social cognition, including facial emotion recognition, prosocial behavior such as trust and sharing as well as empathy (Deckers et al., 2015; von Dawans et al., 2012; Wolf et al., 2015). These findings are compatible with the “tend-and-befriend” hypothesis (Buchanan and Preston, 2014; Taylor et al., 2000), which states that, in addition to the “fight-and-flight” model, enhanced prosocial behavior after stress is a reasonable response pattern.

In terms of MR function, animal studies support the hypothesis that MR are strongly involved in social cognitive processes (Ter Horst et al., 2014). For instance, MR deficient mice and mice after MR blockade were less able to discriminate between familiar and unfamiliar mice. The high density of MRs in the hippocampus, amygdala and prefrontal cortex have been suggested to be responsible for these effects (Ter Horst et al., 2014).

Again, human studies on this topic are rare. We investigated the role of MR in empathy, an important aspect of social cognition. Empathy consists of at least two components: a cognitive component, which captures the capacity to infer others’ mental states (Zaki and Ochsner, 2012), and an affective component, which reflects an observer’s emotional response to another person’s emotional state (Blair, 2008). In our studies, we used the “Multifaceted Empathy Test” (MET) (Dziobek et al., 2008), a well validated task to assess cognitive and emotional empathy. In one study, we administered spironolactone before the participants were tested with the MET. No differences compared to placebo could be revealed in healthy individuals after spironolactone administration, neither in emotional nor cognitive empathy (Wingenfeld et al., 2016).

However, a different picture emerged after MR stimulation, which led to greater emotional empathy but not cognitive empathy compared to placebo (Wingenfeld et al., 2014). This raises the question why the enhancing effects of MR stimulation are only seen on emotional but not cognitive empathy. One might argue again that MR are highly expressed in limbic brain areas, which are strongly involved in the processing of emotional information (Groeneweg et al., 2012; Joels et al., 2011). In addition, it is unclear why MR stimulation but not blockade affects emotional empathy. Possibly, under basal condition MR are not strongly involved in emotional empathy. During stress, however, it might be important to become affectively involved, a process to which MR likely contribute. This fits to our finding that MR stimulation leads to attentional bias to sad faces, whereas under placebo sad faces were avoided (Schultebraucks et al., 2016a). Possibly, stronger attention towards emotional faces might facilitate emotional empathy.

Clearly, these interprestation are speculative and these first results need replication. Furthermore, other facets of social cognition should be additionally investigated in the future.

## 3. Mineralocorticoid receptor function and cognition in stress-associated disorders

Dysfunctions in hypothalamic-pituitary-adrenal (HPA) axis have been reported for several mental disorders. Major depressive disorder (MDD) is characterized by increased cortisol release in concert with reduced feedback sensitivity of the HPA axis, which has been mostly attributed to altered GR function (Holsboer, 2000; Parker et al., 2003). Indeed, there is compelling evidence for altered GR function in MDD, with studies including measurements of GR mRNA, GR gene polymorphisms and methylation of the GR gene promoter (Binder et al., 2004; McGowan et al., 2009; Otte et al., 2009; Webster et al., 2002). However, fewer studies in MDD have focused on MR, although there is evidence of decreased MR expression in the hippocampus and prefrontal cortex (Klok et al., 2011a; Medina et al., 2013), brain regions crucially involved in cognitive and emotional function.

In borderline personality disorder (BPD) GR gene methylation status has been measured suggesting a dysfunction of the GR (Martin-Blanco et al., 2014; Steiger et al., 2013). However, in one of our own studies we measured steroid sensitivity, i.e., the ability of corticosteroids to inhibit T cell proliferation and did not find any differences between BPD patients and controls in MR and GR sensitivity (Fischer et al., 2014). Again, almost no study has assessed MR function in these patients.

### 3.1. Major depressive disorder

Patients with major depression often exhibit cognitive deficits. Several recent meta-analyses have shown that memory and executive function are among those domains that are most consistently impaired in depressed patients (Bora et al., 2013; Rock et al., 2014; Wagner et al., 2012). Furthermore, studies investigating autobiographical memory have consistently described the phenomenon of “overgeneral autobiographical memory” in MDD patients, with memories of events of their past in categories rather than retrieving a single episode (Williams et al., 2007).

Importantly, several groups have found impaired cognition to be associated with elevated cortisol in patients with major depression (Behnken et al., 2013; Gomez et al., 2006; Hinkelmann et al., 2009, 2013; O’Hara et al., 2007) although not all studies concur (Krogh et al., 2012). Decreased GR sensitivity leading to high cortisol and impaired cognitive function have been rather consistently described in major depression (Holsboer and Ising, 2010; Otte et al., 2016; Pariante and Lightman, 2008; Schatzberg, 2015). However, less is known about the role of MR in cortisol secretion and cognitive function in depression (Murck et al., 2014).

In the recent years, several studies suggested an important role of MR on cognitve function in depressed patients. First, there is evidence from post-mortem studies that MDD patients exhibit decreased MR expression in hippocampus and prefrontal cortex (Klok et al., 2011a; Medina et al., 2013; Qi et al., 2013) and several polymorphisms and

haplotypes of the MR gene (NR3C2) have been associated with depression (Klok et al., 2011b). Furthermore, variations in the MR gene are associated with negative memory bias and amygdala reactivity and these associations appear to be influenced by life adversity (Bogdan et al., 2012; Vinkers et al., 2015; Vogel et al., 2014). Further, GR blockade with mifepristone improved cognitive function in bipolar depressed patients and the authors speculated that this might be due to an increased MR-mediated signal (Watson et al., 2012). In another study, an association between a polymorphism of the MR gene and emotional memory has been show in remitted MDD patients, especially in those with childhood trauma (Vrijsen et al., 2015). Additional evidence suggests that polymorphisms of the MR gene are associated with memory performance in a sample of healthy individuals and depressed patients (Keller et al., 2017). These study provide evidence for an important role of MR function in cognitive and emotional function in patients with MDD.

Because of the clinical importance of cognitive symptoms in MDD, which lead to high individual burden, it is of particular interest to investigate whether stimulation of MR function improves cognitive performance in these patients as shown for healthy individuals. In a first study, we compared relatively young medication-free patients with MDD to healthy controls of the same age and found improved verbal memory and executive function after fludrocortisone compared with placebo across groups (Otte et al., 2015a) (see also Fig. 2).

In contrast to younger depressed patients, older MDD patients performed worse in verbal learning and visuospatial memory after fludrocortisone (Otte et al., 2015b). As mentioned above, in healthy individuals no such differences were observed between young and elderly participants, which both performed better after MR stimulation (Hinkelmann et al., 2015). Specificity of autobiographical memory retrieval was not affected by MR stimulation, neither in patients with MDD nor in healthy controls (Fleischer et al., 2015). In sum, there are too few studies to draw final conclusions on the association between cognition and MR functioning in MDD. Importantly, the MDD population is heterogenous and there are subgroups such as patients psychotic symptoms or treatment resistance, which showed the most pronounced MR alterations (Juruena et al., 2013; Lembke et al., 2013).

Studies that examined social cognition in MDD have revealed equivocal results (Schreiter et al., 2013) and almost no studies on the association between stress hormones and social cognition have been conducted in depressed patients. However, we recently found that patients with MDD had higher cognitive empathy scores compared to controls in the placebo condition but not after administration of spironolactone. In other words: MR blockade reduced cognitive empathy in MDD patients but not in healthy controls (Wingenfeld et al., 2016). No such effect was seen for emotional empathy. Thus, a "normalisation" of enhanced cognitive empathy seems to occur in the MDD group in response to MR blockade. Furthermore, cognitive empathy was positively correlated with depression scores after placebo. These results contrast the idea that empathy is a protective factor for mental health per se. Rather, our results are in line with the hypothesis that „excessive "cognitive empathy in some circumstances is maladaptive and might be linked to the development of internalizing disorders (Tone and Tully, 2014). This fits to a study by Wolkenstein and colleagues, who found better performance in the "Reading the Mind in the Eyes test" in depressed patients compared to controls (Wolkenstein et al., 2011).

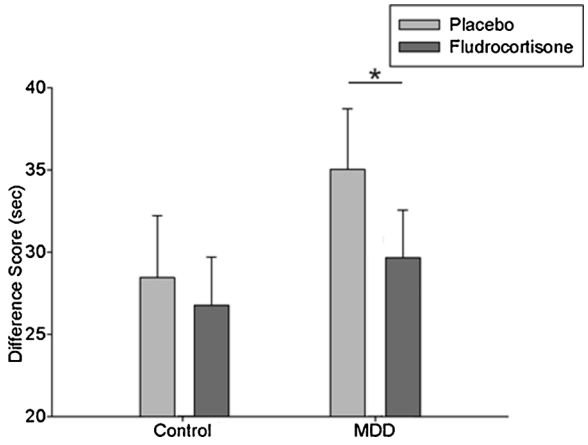


**Fig. 2.** Effects of MR stimulation with fludrocortisone on executive function as measured with the Trail Making Test (difference score: TMT B minus TMT A in seconds) in healthy participants and patients with major depressive disorder (MDD). Both group performed faster after fludrocortisone compared to placebo (sign. main effect treatment, p = .04) (From: Otte et al., 2015a).

### 3.2. Borderline personality disorder

Borderline personality disorder (BPD) is characterized by stress-associated symptoms and alterations in the HPA axis have been frequently reported in these patients (Wingenfeld et al., 2010; Wingenfeld and Wolf, 2015). Similar to our studies in healthy individuals and patients with MDD, we administered fludrocortisone and placebo before cognitive testing. In female patients with BPD, but not in healthy women, we found that MR stimulation impaired verbal memory and visuospatial memory (Wingenfeld et al., 2015). In contrast, working memory was improved after fludrocortisone compared to placebo in both groups. Thus, in BPD impairing effects of MR stimulation were seen on hippocampus-mediated memory processes, an effect opposite to healthy controls, in whom fludrocortisone improved memory. Interestingly, these differences between BPD and controls seem to be relatively specific for hippocampus-associated cognitive domains, since there were no such differences in more prefrontal cortex-related working memory.

In a previous study, we investigated the effects of hydrocortisone administration on cognition in BPD. We found that this simultaneous stimulation of MR and GR resulted in an opposite pattern, namely improved memory retrieval after hydrocortisone administration but unaffected executive function (Carvalho Fernando et al., 2013; Wingenfeld et al., 2013). Taken these results together, it seems that in BPD patients hippocampus-based memory benefits from GR stimulation but is impaired after MR stimulation.

Because many symptoms in BPD patients occur within social contexts, it has been assumed that BPD is characterized by aberrant social cognition (Lazarus et al., 2014; Roepke et al., 2012). However, experimental findings remain equivocal, suggesting either impaired social cognition, no alterations or even better performance in BPD patients compared to healthy controls (Dinsdale and Crespi, 2013; Lazarus et al., 2014; Roepke et al., 2012). With respect to empathy measured with the MET, we did not find any significant differences between BPD patients and healthy controls in two independent studies (Wingenfeld et al., 2018, 2014). After administration of fludrocortisone, we found that similar to healthy controls emotional empathy but not cognitive empathy was enhanced in BPD (see Fig. 3) (Wingenfeld et al., 2014). Interestingly, a different picture occurred after exposure to psychosocial stress (Wingenfeld et al., 2018). We randomized BPD patients and healthy controls to either the Trier Social Stress Test (TSST) or a control condition before the MET was performed. While there were no group differences after the control condition, BPD patients had significantly lower emotional empathy scores after stress compared to healthy individuals (see Fig. 3). There were no such effects for cognitive empathy. We interpreted these findings as a stress-induced "fight-and-flight" response pattern in patients with BPD resulting in an inhibition of prosocial behaviour (see for Wingenfeld et al., 2018 for detailed discussion). This effect seems to be mediated by other mechanisms than MR activation, such as alterations of GR function or other stress-induced physiological changes, for example altered noradrenergic activation after psychosocial stress. Of note, BPD patients are highly sensitive to social rejection and negative evaluation (Chapman et al., 2014; Renneberg et al., 2012). Thus, the lack of feedback from the audience

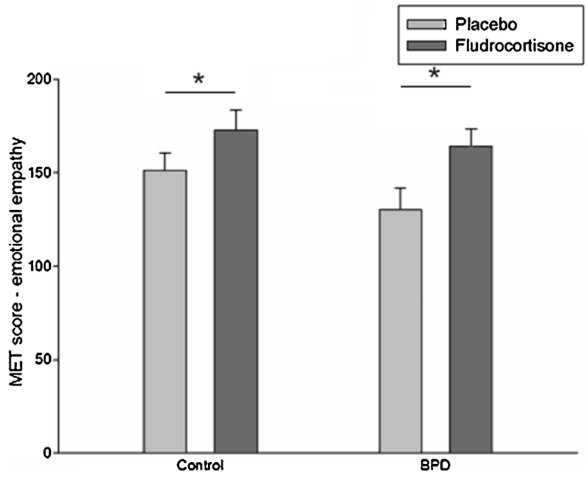


**Fig. 3.** Effects of MR stimulation with fludrocortisone on emotional empathy in healthy participants and patients with borderline personality disorder (BPD). Both group had higher scores on emotional empathy after fludrocortisone compared to placebo (From: Wingenfeld et al., 2014).

within the TSST might be particularly aversive for BPD patients.

In sum, it has been shown that MR stimulation has beneficial effects on cognition not only in healthy individuals but also in depressed patients. In previous studies, we found that patients with MDD did not show the well-described impairments in memory retrieval after hydrocortisone administration (Terfehr et al., 2011a, b), which is in line with findings of GR dysfunction in MDD. Thus, MDD might be characterized by intact MR function in concert with reduced GR sensitivity in MDD. However, because the cognition-improving effects of MR stimulation were not seen in elderly depressed patients (Otte et al., 2015b), future research should further investigate subgroups of MDD with respect to age, sex and subtype of MDD such as melancholic, atypical and anxious depression.

In borderline patients, the picture seems to be more complex and the effects of MR stimulation appear to be task specific. We found that BPD patients performed worse after fludrocortisone administration compared to placebo in visuospatial and verbal memory, while working memory was improved after MR stimulation. Interestingly, in an additional study, we found that administration of hydrocortisone had enhancing effects on memory retrieval in BPD patients (Wingenfeld et al., 2013). Thus, both pharmacological treatments (fludrocortisone and hydrocortisone) affected hippocampal-based memory such as episodic memory retrieval in an opposite direction compared to healthy controls.

## 4. Discussion

As outlined above, a plethora of animal and human studies have now confirmed an important role of MR in physiological cognitive and emotional function (de Kloet et al., 2016; ter Heegde et al., 2015). In healthy humans, the most consistent findings after blockade of MR are impaired visuospatial memory and impaired selective attention as indicated by several studies and no contradicting study (Table 1) (Cornelisse et al., 2011; Otte et al., 2007; Rimmele et al., 2013). In contrast, verbal learning and verbal memory retrieval seem not to be affected by MR blockade (Cornelisse et al., 2011; Otte et al., 2007; Rimmele et al., 2013; Young et al., 2016).

In paradigms using MR stimulation, verbal learning and verbal memory consolidation as well as visuospatial memory retrieval was improved in healthy individuals (Table 2) (Groch et al., 2013; Hinkelmann et al., 2015; Piber et al., 2016). Furthermore, preliminary evidence from single studies suggest an important role of MR on selective attention after emotional stimuli (Schultebraucks et al., 2016a), on decision-making (Deuter et al., 2017), and on emotional empathy (Wingenfeld et al., 2014), important aspects of social cognition.

Thus, animal data and studies from healthy individuals converge such that MR play an important role in the (selective) appraisal of new situations and the following response selection, for which decision-making and empathy in emotional contexts are important determinants. Furthermore, MR are crucially involved in visuospatial navigation and memory whereas the exact role of MR in verbal learning and verbal memory needs to be further characterized. This seems all the more important as one study in obese individuals who were continously treated with low-dose spironolactone over 6 weeks showed improved rather than impaired hippocampus-dependent paired-associated learning adding to the complexity of the association between MR and cognition (Rotenstein et al., 2015). Since it is well-known that obesity is associated with increased MR activity in peripheral tissues and possibly in central tissues as well (Infante et al., 2017), it is possible that in conditions with mineralocorticoid excess blocking MR rather than stimulating MR exerts beneficial effects on cognition. However, other potential reasons for these findings include the mode and dosage of spironolactone administration (single dose vs. continuous administration over six-weeks; high versus low-dose).

Importantly, aging might also affect the association between MR function and cognition because animal studies have demonstrated largely reduced MR expression in the hippocampus of aged dogs (Choi et al., 2008; Reul et al., 1991). However, when comparing young (mean age 25.4 ± 4.6 years) and elderly (mean age 63.2 ± 8.2 years) healthy individuals we found – as expected – that young participants performed significantly better than elderly individuals in memory tasks. However, in both groups fludrocortisone improved visuospatial memory (Hinkelmann et al., 2015). The relatively young age of the group of elderly participants might be one reason why we did not find differential age effects in this study.

However, in contrast to studies in healthy participants, age did affect the effects of fludrocortisone on cognition in depressed patients. In young depressed patients fludrocortisone exerted beneficial effects on verbal memory and executive function (Otte et al., 2015a), whereas in elderly depressed patients MR stimulation with fludrocortisone led to impaired verbal learning and visuospatial memory (Otte et al., 2015b) (Fig. 4). Potentially, there is a depression by age interaction that affects the association between MR function and memory and further studies should systematically disentangle age and depression effects.

In any event, there is evidence that major depression is associated with decreased expression of MR in several brain regions (Klok et al., 2011a; Lopez et al., 1998; Medina et al., 2013; Qi et al., 2013). In turn, several animal studies have consistently shown that antidepressants up-regulate MR in the brain and that this effect is present across antidepressant classes (Bjartmar et al., 2000; Reul et al., 1993; Seckl and Fink, 1992; Yau et al., 2002). Importantly one study in depressed patients found that fludrocortisone add-on to standard antidepressants accelerated the response in the group of responders by about one week (Otte et al., 2010). However, no additional benefit of MR stimulation over SSRI treatment alone on cognitive function was observed in that study (Hinkelmann et al., 2012). In contrast, a study using mifepristone, a glucocorticoid receptor antagonist that shifts the MR/GR balance towards MR (Block et al., 2018) improved cognitive function in bipolar depression (Young et al., 2004).

In summary, there is ample evidence that depressed patients exhibit reduced MR expression in several brain regions and that antidepressants up-regulate MR (ter Heegde et al., 2015). Due to the high density of GR and MR in the hippocampus, this brain structure is thought to be a sensitive region for the effects of GCs (de Kloet et al., 2005). Of note, in patients with MDD as well as BPD, there are several structural imaging studies, suggesting hippocampal volume reduction (Bremner et al., 2000; Wingenfeld et al., 2010), and several factors as childhood trauma and illness duration seem to be associated with a smaller hippocampal size as well (Heim and Binder, 2012). One might

**Table 2**
Effects of MR stimulation with fludrocortisone on cognition in healthy individuals.

| Study (Dosage) | Encoding | Verbal memory retrieval | Visuo-spatial memory | Working memory | Autobiogra-phic memory | Selective attention | Executive function | Empathy |
|---|---|---|---|---|---|---|---|---|
| Groch et al., 2013 (0.2 mg) | enhanced | | | | | | mirror tracing: No effect | |
| Wingenfeld et al., 2014 (0.4 mg) | | | | | | | | emotional empathy: enhanced; cognitive empathy: no effect |
| Hinkelmann et al., 2015 (0.4 mg) | word list: enhanced | word list after 30 m in. no effect | enhanced | enhanced | | | | |
| Otte et al., 2015a, 2015b (0.4 mg) | | | | | | | trail making test: no effect | |
| Fleischer et al., 2015 (0.4 mg) | | | | | no effect | | | |
| Piber et al., 2016 (0.4 mg) | | | Retrieval: enhanced; learning: unaffected | | | | | |
| Schultebraucks et al., 2016a, 2016b (0.4 mg) | | | | | | Emotional dot probe: enhanced to negative faces | | |
| Deuter et al., 2017 (0.4 mg) | | | | | | | Risky decision: enhanced | |

*in this studies healthy individuals were compared to patients with major depressive disorder, part of the healthy sample was overlapping with Hinkelmann et al., 2015 paper, thus only results not presented in Hinkelmann et al., 2015 were considered in the table.

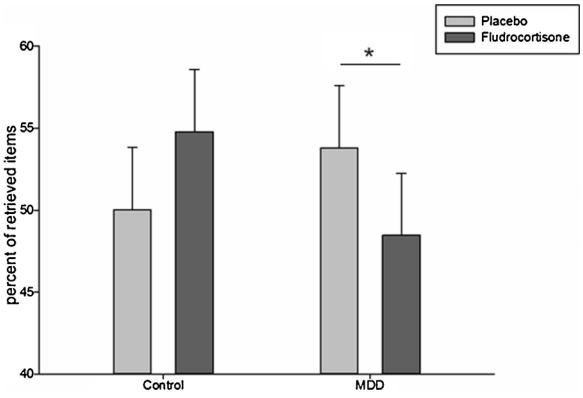


**Fig. 4.** Effects of MR stimulation with fludrocortisone on visual-spatial memory as measured with the Rey/Taylor Figure in a sample of elderly healthy and depressed participants. Y-axis depicts % of retrieved items. Elderly healthy participants performed better, while elderly depressed patients showed reduced memory retrieval after fludrocortisone compared to placebo (sign. interaction effect between treatment and group, p = .02) (From: Otte et al., 2015a, 2015b).

suggest that disturbances in hippocampal integrity might be a non-specific risk factor for the development of psychiatric disorders and might contribute to altered cognitive function.

In terms of MR function and cognition, a study in children and adolescents with lymphoblastic leukemia is of great clinical importance (Warris et al., 2016). That study examined whether add-on hydrocortisone would ameliorate cognitive and emotional side effects of dexamethasone therapy as part of the leukemia treatment. Dexamethasone as a highly potent GR agonist causes suppression of cortisol secretion, and thus results in depletion of the brain MR of endogenous cortisol. This could be responsible for some of the cognitive and emotional side effects of dexamethasone (Meijer and de Kloet, 2017). Indeed, the study demonstrated that add-on hydrocortisone to DEX attenuated side effects of dexamethasone (less emotional problems, better memory performance) compatible with the MR/GR balance concept (Meijer and de Kloet, 2017). Accordingly, these findings have great implications beyond leukemia and are highly relevant for endocrine disoders associated with impaired or abolished cortisol secretion as in patients with adrenal insufficiency (Addison's disease) but also in patients with hypercortisolemia as in Cushing's disease. Importantly, both disorders are associated with cognitive and emotional problems (Schultebraucks et al., 2015, 2016b; Starkman, 2013; Tytherleigh et al., 2004) and interventions to restore the MR/GR balance might be promising approaches not only in these disorders but also in stress-associated psychiatric disorders with more subtle endocrine alterations.

Another potential clinical approach stems from our preliminary finding of enhanced emotional empathy after MR stimulation with fludrocortisone in women with borderline personality disorder and in healthy women. These "pro-social" effects resemble those of oxytocin, for which not only a prominent role in BPD has been proposed but which is already being used in clinical trials to augment psychotherapy effects (Flanagan et al., 2018; Koch et al., 2014). Thus, it is a testable hypothesis whether exogenous MR stimulation as an add-on treatment

**Box 1**
Questions for the future

Are there differential effects of nucleus vs. membrane receptors and to what extent are these receptors involved in fast non-genomic vs. slow genomic effects on cognition?

In which context/cognitive domain does stimulating or blocking the MR have beneficial or adverse effects on cognition in health and disease?

And to what extent does this depend on moderators such as age, sex, or obesity?

Can exogenous MR stimulation as an add-on treatment enhance the beneficial effects of psychotherapy and antidepressants?

enhances the beneficial effects of psychotherapy.

In sum, given the important role MR play in cognitive and emotional function (de Kloet et al., 2016; ter Heegde et al., 2015; Vogel et al., 2016), further studies on this topic in stress-associated disorders such as MDD, PTSD, or BPD, in endocrine disorders such as Addison's disease and Cushing's disease, and in disorders requiring high doses of glucocorticoids appear clearly warranted (Box 1).

## Conflict of interest

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

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