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The Role of the Mineralocorticoid Receptor for Cognitive Function, Mood and Social Cognition

– An Examination in Patients with Primary Adrenal Insufficiency and in Healthy Subjects –

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English summary

Stress-exposure leads to a boost of cortisol that acts via the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). Evidence shows that stress influences cognitive performance and emotion processing. During stress, the MR is important for appraisal and emotion regulation, whereas the GR is crucial for reallocation of energy, which is important for the modulation of behavior and memory processes. The MR and GR work together in a complementary way. Imbalances due to chronic stress and depression can result in altered cognitive and emotional processes, especially in reaction to stress-exposure.

The objective of this dissertation project is to help disentangle the complex interaction of the MR and the GR. Since previous studies have first and foremost examined the role of the GR, the role of the MR is understudied, despite the fact that novel preclinical and clinical studies have shown that the MR plays a crucial role on cognitive functioning and emotional processes. The aim of the present dissertation is to extend the existing body of knowledge with regard to whether and how human MR occupation influences cognitive functioning, mood and social cognition in patients with Addison's disease and in healthy participants. The following research questions are examined:

1) Is the state-of-the-art hormone replacement therapy with synthetic MR and GR agonists in patients with Addison's disease on a par with normal endogenous cortisol of healthy subjects with regard to neuropsychological function?
2) What are the acute effects of high MR occupation compared to low MR occupation with regard to neuropsychological functions, in particular, with regard to prefrontal cortex- and limbic structure-related functions like cognition and mood in patients with Addison's disease?
3) What is the role of the MR on more specialized domains like social cognition in young healthy subjects?

To investigate cognitive functioning and mood in patients with Addison's disease we used a well-established neuropsychological test battery that comprised verbal memory, visual-spatial memory, executive function, attention, working memory and autobiographical memory. To examine the role of the MR on social cognition, i.e.

selective attention and emotion recognition, we used the emotional dot-probe task as well as the facial emotion recognition task.

The main results of the dissertation are, first, that long-term hormone substitution with fludrocortisone and hydrocortisone in patients with Addison's disease has no influence on cognitive performance, except on verbal learning. Second, high MR occupation has beneficial effects on cognitive performance in verbal memory and on a trend level on attention and executive function as well as beneficial effects on self-reported mood in patients with Addison's disease, even when the daily dose of fludrocortisone was skipped only once. Third, selective MR stimulation with the potent MR-agonist fludrocortisone results in a shift of selective attention towards sad faces in healthy subjects. However, MR stimulation has no beneficial effect on emotion recognition.

In sum, the present studies corroborate previous findings on MR functioning in preclinical studies and in humans, e.g. in depressed and healthy participants. However, this dissertation presents these effects for the first time in patients with lack of endogenous cortisol. The results indicate that high MR occupation is beneficial for cognitive functioning and mood. Moreover, the MR seems to play a crucial role in quick automatic emotional processing, meaning a shift in selective attention towards negative emotional cues after MR stimulation.

Deutsche Zusammenfassung (German summary)

Stress führt zu einer Ausschüttung von Kortisol, das über den Mineralocorticoidreceptor (MR) und den Glucocorticoidreceptor (GR) wirkt. Forschungsergebnisse zeigen, dass Stress die kognitive Leistungsfähigkeit sowie emotionale Reaktionen beeinflusst. Bei Stress spielt der MR eine wichtige Rolle für die Bewertung der Situation und für die Regulation von Emotionen. Der GR hingegen ist wichtig für die Umverteilung metabolischer Energie und die Verhaltensanpassung sowie für Gedächtnisprozesse. Der MR und der GR arbeiten zusammen und ergänzen sich gegenseitig. Chronischer Stress und Depression können zu einem Ungleichgewicht zwischen MR und GR und somit zu einer veränderten Stressreaktion führen sowie zu veränderten kognitiven und emotionalen Prozessen.

Gegenstand der vorliegenden Dissertation ist es, das komplexe Zusammenwirken von MR und GR weiter zu untersuchen. Bisherige Studien habe insbesondere die Rolle des GR erforscht. Tierstudien und erste klinische Studien konnten aber zeigen, dass der MR eine wichtige Rolle bei kognitiven Funktionen und bei Emotionen spielt. Ziel der vorliegenden Dissertation ist es, den bereits existierenden Wissensstand zu erweitern und zu untersuchen, welchen Einfluss der MR auf kognitive Funktionen, die Stimmung und soziale Kognition bei Patienten mit Morbus Addison und bei gesunden Probanden ausübt. Dabei ergeben sich folgende Fragestellungen:

1) Welchen Einfluss hat die langjährige „state-of-the-art“ Substitutionstherapie mit synthetischen MR- und GR-Agonisten bei Patienten mit Morbus Addison auf die kognitive Leistungsfähigkeit im Vergleich zu normaler endogener Kortisolausschüttung bei gesunden Probanden?
2) Welchen Einfluss übt eine hohe MR Besetzung im Vergleich zu einer geringen MR Besetzung auf die kognitive Leistungsfähigkeit und die Stimmung bei Patienten mit Morbus Addison aus?
3) Welchen Einfluss hat eine MR Stimulierung auf komplexere psychologische Funktionen wie die soziale Kognition?

Um diese Fragestellungen zu untersuchen, wurde eine gut etablierte neuropsychologische Testbatterie eingesetzt, die das verbale Gedächtnis, das visuell-räumliche Gedächtnis, die Exekutivfunktion, Aufmerksamkeit, das Arbeitsgedächtnis sowie das autobiographische Gedächtnis umfasste. Um den Einfluss des MR auf

soziale Kognition zu untersuchen, wurden ein emotionales Dot-Probe-Paradigma und eine Emotionserkennungsaufgabe verwendet.

Wichtige Hauptbefunde waren erstens, dass eine jahrelange Hormonsubstitution keinen nachteiligen Einfluss auf die kognitive Leistungsfähigkeit von Patienten mit Morbus Addison im Vergleich zu gesunden Kontrollprobanden hatte, außer im Bereich des verbalen Gedächtnisses. Dies konnte gezeigt werden, trotz einer durchschnittlich seit ca. 18 Jahren (SD = 11) andauernden Erkrankung und Behandlung mit Hydro- und Fludrocortison. Trotzdem war die selbstberichtete Lebensqualität von Patienten mit Morbus Addison im Vergleich zu gesunden Probanden signifikant beeinträchtigt. Zweitens zeigten Patienten mit Morbus Addison bei hoher MR Besetzung eine bessere kognitive Leistungsfähigkeit (verbales Gedächtnis, Aufmerksamkeit und Exekutivfunktion) und eine bessere Stimmung im Vergleich zu einer geringen MR Besetzung; Und dies, obwohl die reguläre Fludrocortisoneinnahme nur einmal ausgelassen wurde. Drittens führte die akute MR Stimulierung bei Gesunden zu einer gesteigerten selektiven Aufmerksamkeit für traurige Gesichter. Hingegen scheint der MR keine Rolle bei der Emotionserkennung zu spielen.

Die vorliegenden Befunde bekräftigen die Ergebnisse früherer Untersuchungen zur Rolle des MR. Zudem konnten die Studien dieser Dissertation zeigen, dass dies auch auf Patienten zutrifft, die kein endogenes Kortisol bilden (d.h. bei Patienten mit Morbus Addison). Die Ergebnisse unterstreichen, dass eine hohe MR Besetzung zu einer besseren kognitiven Leistungsfähigkeit und Stimmung führt. Zudem konnte gezeigt werden, dass der MR eine wichtige Rolle bei der Regulierung von schnellen, automatischen Verarbeitungsprozessen spielt, wie bei der selektiven Aufmerksamkeit.

1 Theoretical and empirical background

Psychoneuroendocrinology is a young multidisciplinary research field that integrates basic research of psychology, psychiatry, neurology, endocrinology, immunology, and neurobiology. Its objective is to examine the intricate interrelations of stress with various psychological and biological factors in order to shed light on the clinical implications of the stress response for neuropsychiatric disorders and mental processes in general. The roots of psychoneuroendocrinology can be traced back to ancient times, when Hippocrates (469–399 B.C.) and Galen (A.D. 129–200) famously related the four bodily fluids known as *humors* with mental phenomena they classified as *sanguine*, *choleric*, *melancholic* and *phlegmatic temperaments* (Wolkowitz & Rothschild, 2008). Although this may be seen as an early attempt to link hormones and behavior, the emergence of modern psychoneuroendocrinology took place only after the development of the concepts of *stress*, *homeostasis*, and the so-called *fight-flight-response* through the physiology of a *sympathico-adrenal medullary system* by Walter Cannon in 1915 (Wolkowitz & Rothschild, 2008). Revised and scientifically updated versions of such concepts still influence research on stress, cortisol and their psychological effects today, although the sophistication of the field has long reached genetic and molecular levels of differentiation.

One interesting and innovative research area is the investigation of the mineralocorticoid receptor. Besides the well-known glucocorticoid receptor (GR), the mineralocorticoid receptor (MR) is one of two main receptors in the brain on which the hormone cortisol acts. The role of MR functioning is a new and largely unexplored target in psychoneuroendocrinological research. Still, rather little is known about the psychological effects of the stress hormone cortisol as a function of MR occupation. The topic of this dissertation is to examine the role of MR functioning on neuropsychological domains like mood, cognition and social cognition. On the one hand, this is achieved by investigating the effects of MR occupation on mood and cognition in patients who lack sufficient endogenous cortisol and aldosterone (primary adrenal insufficiency, i.e. Addison's disease). On the other hand, the role of MR functioning on social cognition is explored by examining the effect of acute MR stimulation on selective attention and facial emotion recognition in healthy subjects.

Together, these findings close an important gap in the research of MR functioning. They also extend the existing body of knowledge regarding the link between cortisol effects in the brain and the modulation of behavior, mood or social cognition.

As will become clear below, MR function is a fascinating, but also a very complex matter. The first source of complexity is the interaction of MR with GR effects that has been investigated as part of the so-called MR/GR balance hypothesis (de Kloet, 1991; de Kloet, Joëls, & Holsboer, 2005; de Kloet, Vreugdenhil, Oitzl, & Joëls, 1998). This hypothesis gives rise to several intriguing questions. How do different ratios of MR to GR imbalances affect some particular cognitive or affective domain? What ratio of MR to GR occupation is best for optimal function of the respective domain? What are the isolated effects of MR (or GR) stimulation in contrast to MR (or GR) blockage? The second source of complexity derives from the fact that the cognitive and affective consequences of cortisol receptor occupation is not merely a question of balance between MR and GR, but rather an intricate function of time. It is therefore necessary to discriminate rapid effects (within seconds to minutes) from slow effects (taking several hours) of both MR and GR occupation. In order to unravel the specific effects of cortisol receptor occupation on behavioral, cognitive or affective domains, it is therefore indispensable to take into account the differential influence of GR and MR receptors as well as the specific timing of their effects (Joëls, Sarabdjitsingh, & Karst, 2012).

Previously, the role of GR function has been the main target of interest concerning the effects of cortisol release (e.g. effects resulting from different sorts of stressors like psychosocial stress, chronic stress, etc.). Many of these studies have shown that the GR plays a crucial role on cognitive functioning (de Kloet, 2014; de Kloet et al., 2005; de Kloet, Oitzl, & Joëls, 1999). Only recently studies have begun to also emphasize the role of MR occupation on cognitive domains (Joëls, Karst, DeRijk, & De Kloet, 2008). Since the MR is the central topic of this dissertation, the main insights from previous research will be comprehensively presented in section 1.2 and 1.3. Moreover, the current knowledge on MR effects and their timing is elucidated in section 1.3.1 and 1.3.2. These introductory remarks will answer the questions: “What do we already know about the role of MR function and psychological variables like cognition, mood and social cognition?” and “What do we still not know?”

Because the presently available findings on MR function are still fragmentary, this dissertation was designed to address ensuing research questions that arise from the current body of knowledge. In section 2, these research questions and corresponding hypotheses are specified in detail. This will answer the question: "Why is it promising to examine the role of *the MR* on the respective neuropsychological functions?"

Finally, section 2.2 outlines how the three studies, contained in the present dissertation project, were designed to answer these research questions as well as to assess the respective hypotheses. This will provide an answer to the question of method: "What measures did we use to examine the role of the MR on the neuropsychological functions?" It will also illustrate that we used randomized, matched and blinded treatment studies and how we did so. But before we delve into these topics, some very short remarks concerning the broader context of stress, cortisol and the relation to MR function are in place.

1.1 The neuroendocrine stress response and its relation to MR and GR

An influential account of stress is the so-called transactional model of stress going back to Richard Lazarus' seminal works. Lazarus writes: "*Stress arises when individuals perceive that they cannot adequately cope with the demands being made on them or with threats to their well-being*." (Lazarus, 1966).

The central idea of this account is the concept of appraisal. According to this view, events are stressful only if they are evaluated *as* stressful. This means that any potentially harmful or threatening event like losing a loved one, having an important exam, losing the job or getting a severe illness does not necessarily constitute a stressor, but rather requires the cognitive appraisal *as* being an event that cannot adequately be handled in order to count as a stressor. This appraisal of some event as being stressful can take place within seconds, automatically, and without conscious thinking. Usually two phases of appraisal are distinguished in transactional stress models. A primary appraisal of the external event, and a secondary appraisal of suitable internal coping mechanisms (Lazarus, 1966). Further details concerning the discussion of this or different accounts of stress will be omitted for the purpose of this dissertation. What is more important, is that the MR receptor is thought to play a crucial role in the stress response and the processes of automatic appraisal of events

as stressful as well as in the selection of adequate response strategies (Joëls et al., 2008).

This can be outlined as follows: Acute stress evokes, within seconds, the activation of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA)-axis, which leads to a release of adrenaline, noradrenaline and corticosteroids (de Kloet, 2014; Sandi & Haller, 2015; Ter Heegde, De Rijk, & Vinkers, 2015). The ANS and the HPA-axis work closely together to facilitate an optimal adaptation to varying surroundings (de Kloet et al., 2005). As a consequence, stress causes the release of the corticotropin-releasing hormone (CRH) from the hypothalamus towards the anterior pituitary. This leads to the secretion of the adrenocorticotropic hormone (ACTH) in the anterior pituitary, and ACTH in turn triggers the synthesis and release of corticosteroid hormones from the adrenal cortex (de Kloet et al., 2005).

Corticosteroid hormones (cortisol in humans and corticosterone in rodents) are important for appraisal and decision making in stressful situations and they strengthen cognitive performance, necessary for an adequate stress adaption (de Kloet, 2014). Cortisol is also important for an adequate availability of energy and the attenuation of immune function. Simultaneously, cortisol leads to a negative feedback on the HPA-axis resulting in decreased HPA-axis activity, thereby inhibiting an excessive and detrimental HPA-axis-overactivation (Ter Heegde et al., 2015).

Quite generally, cortisol binds at two different nuclear receptors in the brain, the mineralocorticoid receptor (MR, also known as Type II or NR3C2) and the glucocorticoid receptor (GR, also known as Type I or NR3C1). Whereas the GR is omnipresent across the brain, the MR is mainly distributed in limbic structures, particularly in the hippocampus, the amygdala and the lateral septum (de Kloet, 2014). In comparison to the GR, the MR has a 10-fold higher affinity to cortisol than the GR, i.e. the GR is mainly activated in circadian peaks of cortisol release (such as awakening) or under stress (Ter Heegde et al., 2015). Both the MR and the GR are involved in the negative feedback that inhibits the secretion of cortisol to prevent an HPA-axis-overactivity (de Kloet, 2013). This simplified model of the neuroendocrine stress response and its relation to MR and GR is illustrated schematically in figure 1.

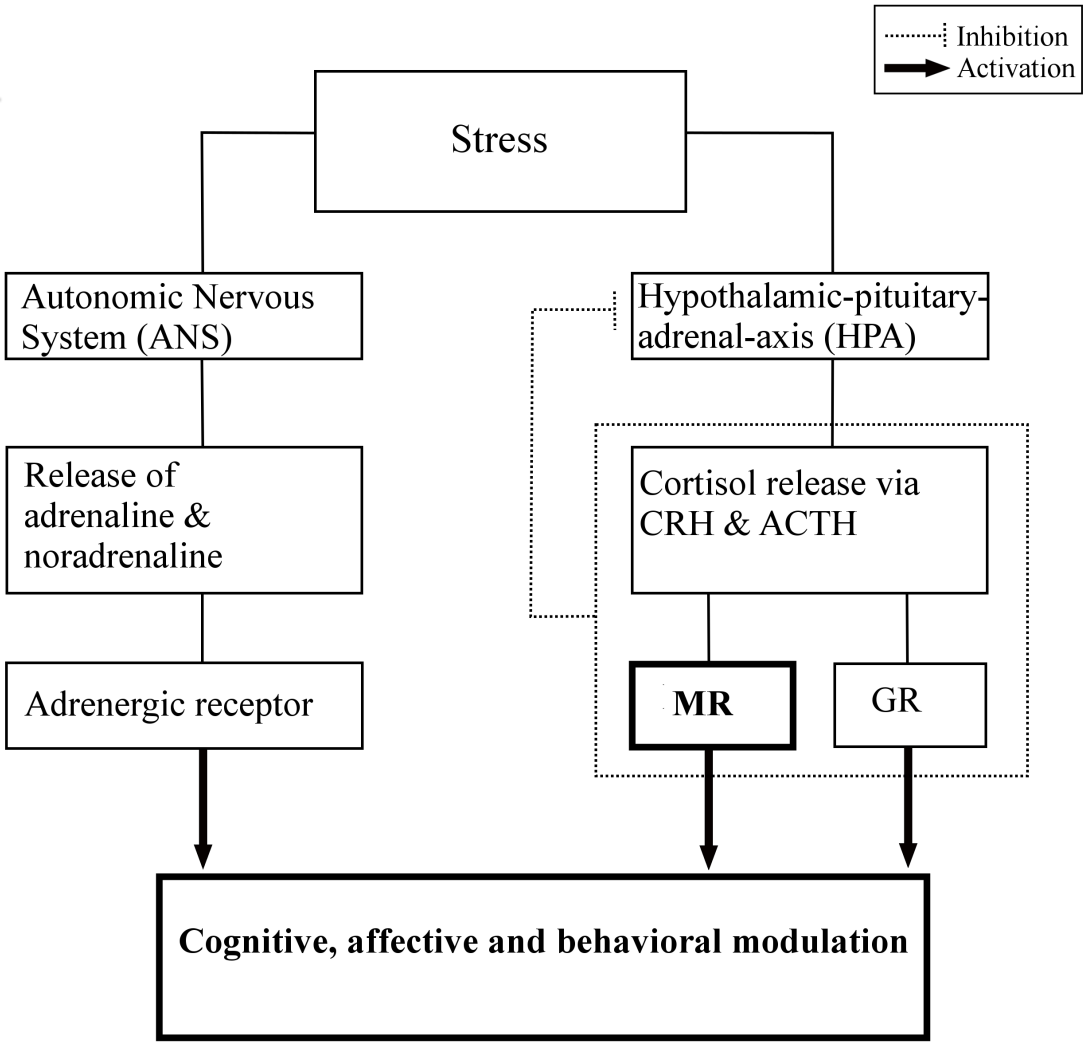

Figure 1. Schematic characterization of the stress response. The left side represents the pathway of the ANS and the right side the pathway of the HPA-axis (activation). On the right side, also the negative feedback of cortisol on the hypothalamus and the pituitary gland is described (inhibition), which leads to a decrease of CRH and ACTH.

The proper functioning of these neuroendocrine mechanisms are important for behavioral, affective and cognitive aspects of neuropsychological domains as well as several medical conditions. For example chronic stress, and as a consequence thereof a persistently and excessively elevated activity of the HPA-axis, can overshoot the *allostatic load*[1] contributing to the development of somatic as well as psychiatric

[1] The term *allostatic load* was introduced by McEwen (2003) and describes the idea that the accumulation of adverse factors is not itself physiologically detrimental. Rather, cognitive appraisal mechanisms (or the lack of adequate) and coping strategies determine the effect of repeated stress exposure, which accumulate over time and only above the body's threshold of the "allostatic load" result in harmful impact on the organism.

disorders (Juster, McEwen, & Lupien, 2010). In addition, traumatic stress is a crucial risk factor for the development of some very prevalent conditions like depression or anxiety disorders (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008).

As concerns its effect on the MR, *acute* stress exposure raises MR expression in the hippocampus (Gesing et al., 2001; A. H. Veenema, Meijer, de Kloet, Koolhaas, & Bohus, 2003). However, *chronic* stress exposure leads to a decrease of the MR expression in the hippocampus and a decreased MR/GR balance (López, Chalmers, Little, & Watson, 1998; Schmidt et al., 2010; A. Veenema, Meijer, De Kloet, & Koolhaas, 2003). This physiological change of reduced MR expression in the hippocampus leads to increased HPA-axis activity after stress-exposure and anxiety (de Kloet et al., 2016). Moreover in patients with depression, research points at a reduction of MR expression in the hippocampus (Klok et al., 2011; Medina et al., 2013), an area of the brain that is known for its importance for memory functions, such as memory consolidation.

In addition, recent studies have shown that the MR plays a crucial role for the appraisal and the selection of response strategies in stressful situations (Oitzl & De Kloet, 1992; Schwabe et al., 2007; Schwabe, Schächinger, de Kloet, & Oitzl, 2010; Schwabe, Tegenthoff, Höffken, & Wolf, 2013). These findings are biologically plausible, since the MR is known to be important for memory and encoding processes for the reuse in future situations in both humans and rodents (Arp et al., 2014; Schwabe, Tegenthoff, Höffken, & Wolf, 2010; Zhou et al., 2010).

From a clinical point of view, it is therefore crucial to elucidate the complex psychoneuroendocrinological interactions underlying stress and cortisol secretion on the one hand, as well as cognitive, affective and social domains of cognition – not only memory – on the other hand.

1.2 The MR/GR balance hypothesis

The *MR/GR balance hypothesis* (de Kloet, 2014; de Kloet et al., 1998; Joëls et al., 2008) postulates that the MR to GR ratio moderates the HPA-axis in a complementary way, in order to adjust for environmental requirements.

On a physiological level, stress leads to an activation of the sympathetic nervous system and the HPA-axis. The resulting activation of MR leads to an

adaptation in the limbic structures of appraisal and recall of information necessary for taking decisions and the selection of response strategies like “fight”, “flight” or “fright”. In contrast, the GR is important for the reallocation of energy to limbic-cortical networks, which is essential for behavioral adjustment and to signal the termination of the stress response (de Kloet, 2014).

Repeated stress-exposure can lead to an MR/GR imbalance. On a behavioral and psychological level, it is thought that imbalances of the MR to GR ratio are associated with cognitive and emotional alteration, especially in response to stress. For example, initial evidence shows that severe stress-exposure, early life events, or prenatal glucocorticoid treatment influence (epi)genetic variations, which seem to effect the MR/GR balance (de Kloet, 2014).

Moreover, cortisol can have positive as well as negative effects on cognitive functioning (Het, Ramlow, & Wolf, 2005), and therefore an inverted U-curve was established that indicates that extraordinary low as well as extraordinary high cortisol levels have adverse effects on cognitive functioning (Het et al., 2005). The MR/GR balance hypothesis can be used to explain this dual role of cortisol acting like a “double-edged sword” (de Kloet, 2014). Within the scope of this hypothesis, previous research has shown that cognitive functioning is improved by high MR occupation and low to moderate GR occupation (de Kloet et al., 1999), which is characteristic for medium cortisol levels, where cognitive performance is enhanced. However, the complex interaction of GR and MR are somehow unclear, due to that fact an isolated investigation of GR and MR is needed.

To disentangle the complex interaction between MR and GR, it is methodologically expedient to examine, in isolation, what role either the blockage or activation of MR or GR play on cognitive and emotional domains. In consequence, there are at least four different approaches: (1) one can block the function of GR, e.g. by inactivating the GR gene in mice (NR3C1-KO mice) or by examining the effects of administration of the GR antagonist[2] mifepristone in humans. (2) One can investigate the function of the GR, e.g. by examining mice with a genetic GR overexpression or by

[2] An antagonist is a pharmacological molecule that binds at the same receptor macromolecule as an agonist (see footnote 3), but does not lead to a biological effect (as opposed to the agonist). The antagonist reduces the action of an agonist. In contrast, a so-called inverse agonist leads to the opposite biological effect than the agonist (Neubig, Spedding, Kenakin, & Christopoulos, 2003).

examining the effects of GR agonist[3] hydrocortisone in humans. (3) One can block the MR function by e.g. inactivating the MR gene in mice (NR3C2-KO mice) or by investigating the effects of the MR antagonist spironolactone in humans. (4) One can examine the function of the MR, e.g. by examining mice with a genetic MR overexpression or by examining the effects of MR agonist fludrocortisone in humans. A fifth possibility is to study medical conditions that result from pathological dysfunction of the GR and the MR in the human organism and to disentangle thereby the specific contribution of either the GR or the MR.

The rationale of the present dissertation is to focus on approach (4) and (5) and will be explained in detail below (section 2.2). Study I of this dissertation project examines the long-term effects of replacement therapy with a MR agonist in Addison's disease on cognitive function and mood (approach 5). Study II compares the acute effects of low vs. high MR occupation in these patients (mixed approach 4 & 5). Study III explores the effect of acute MR stimulation on social cognition in healthy subjects (approach 4).

1.3 The MR in the brain

As has been mentioned above, the MR plays an important role for an adequate stress response and for mental health. Since the function of the MR is the focal point of the present dissertation, it is necessary to present the current state of research concerning MR function in the human brain, especially with regard to the more narrow scope of "limbic MR effects" on particular domains of behavior, cognition and emotion.

The MR has a very high affinity to cortisol and aldosterone (Fuller, 2015). Although aldosterone is the primary mineralocorticoid hormone, its concentration in the human body is 100-fold lower than free cortisol and up to 1000-fold lower than total plasma cortisol (Hawkins, Gomez-Sanchez, Gomez-Sanchez, & Gomez-Sanchez,

[3] An agonist is a pharmacological molecule that acts like a ligand, which binds to a receptor macromolecule and thereby leads to a conformational change effecting a biological response (Neubig et al., 2003).

2012).[4] Cortisol is thus the primary MR ligand in the brain (H.-W. Wang et al., 2016) and the effect of aldosterone on limbic MR stimulation under normal conditions is very limited (de Kloet et al., 2016). In fact, the mineralocorticoid aldosterone plays only a minor role for the MR in limbic areas (Joëls et al., 2012) and the corticosteroid cortisol plays the main role.[5]

Since the MR is also important for the regulation of body fluids as well as for the homeostasis of electrolytes, the MR can also be found outside of the brain e.g. in kidney, colon, sweat glands and heart (Joëls et al., 2008). However, because the studies conducted for this dissertation concentrate on neuropsychological effects of the MR, the following remarks will be limited to the role of MR in the brain.

First, the distribution of the MR (section 1.3.1) and its time-dependent function will be presented (section 1.3.2). Afterwards, the influence of MR on cognitive function will be discussed (section 1.3.3), as well as the influence of MR function on mood (section 1.3.4). Subsequently, it will be outlined what role MR function plays on social cognition (section 1.3.5), and finally, the role of MR in patients with Addison's disease will be illustrate (section 1.3.6).

[4] Free cortisol is the bioactive form of cortisol that is responsible for the physiological function of the hormone. Only about 10% of the circulating cortisol in human serum is free cortisol, 90% is protein-bound (corticosteroid-binding globulin, i.e. CBG, and albumin) (Hamrahian, Oseni, & Arafah, 2004).

[5] A further explanation for the cortisol-preference of the MR in limbic structure like the hippocampus is the absence of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (Odermatt & Kratschmar, 2012). The enzyme 11β-HSD2 acts like a gatekeeper of the MR (Oelkers et al., 1994). It inactivates cortisol into cortisone that is unable to stimulate the MR. Thereby 11β-HSD2 guarantees a local aldosterone-preference of the MR in tissues where it is co-expressed (Wyrwoll, Holmes, & Seckl, 2011). In the human brain, 11β-HSD2 is very restricted, but can be found to some extent in the amygdala and lateral hypothalamus (Holmes & Seckl, 2006), which have been linked to salt appetite and regulation of blood pressure as well as renal function (Hawkins et al., 2012). Thus, the enzyme 11β-HSD2 may protect the MR of these nuclei from insensitivity to aldosterone – even when cortisol concentration is higher – by locally inactivating cortisol via its conversion to cortisone (Wyrwoll et al., 2011).

1.3.1 The distribution of the MR in the brain

As mentioned before, the distribution of the nuclear GR is ubiquitous in the brain with the highest expression in the hippocampus and the paraventricular nucleus of the hypothalamus, whereas there is a more restricted distribution of the nuclear MR.[6] The nuclear MR has a very high expression level in limbic structures, such as in the hippocampus, the amygdala and the lateral septum (de Kloet, 2014; de Kloet et al., 2005). In fact, in the whole human body, the MR has its highest concentration in the hippocampus, namely in the dentate gyrus and CA1-CA4 (Odermatt & Kratschmar, 2012). In consequence, the MR is crucial for the hippocampal function (Hawkins et al., 2012). This is essential since the "hippocampus is the major integrative center for the formation of memories, learning, cognition, and coping with stress"(Hawkins et al., 2012, p. 577).[7] Similarly, the distribution of the membrane-bound MR is thought to be restricted to the hippocampus, amygdala and the hypothalamus (de Kloet, de Jong, & Oitzl, 2008; Groeneweg, Karst, de Kloet, & Joëls, 2012; Joëls et al., 2012).

The limbic brain system is closely associated with emotional information processing (Groeneweg et al., 2012; Joëls, Fernandez, & Roozendaal, 2011). In particular, the amygdala and the lateral septum are closely related to successful stress coping (Singewald, Rjabokon, Singewald, & Ebner, 2011) and to emotions (Rolls, 2015; Sheehan, Chambers, & Russell, 2004). Furthermore, the hippocampus is an important domain for memory and learning processes (Kandel, Schwartz, & Jessell, 2000; Moser & Moser, 1998) and the prefrontal cortex is important for working memory and executive function (Kandel et al., 2000).

In sum, the MR is a very interesting research locus for investigating psychological outcome variables like cognitive function, mood and social cognition, because the brain areas that are closely linked to these psychological phenomena overlap strongly with cerebral structures of highest MR distribution.

[6] For the distinction of nuclear and membrane-bound MR, see the following section 1.3.2.

[7] Besides in limbic structures like the hippocampus, the human MR is also found in the paraventricular nucleus of the hypothalamus (regulating blood pressure and renal function) and the nucleus tractus solitarius (NTS) as well as the cerebral cortex and the Purkinje cells of the cerebellum (the MR function of the latter two are still unknown) (Hawkins et al., 2012).

1.3.2 Time-dependent function of neuronal MR of cell nucleus and membrane

Since cortisol is the main ligand of the MR in limbic brain areas like the hippocampus, time-dependent processes of cortisol release like the circadian rhythm play a decisive role. Normally, there is a peak of cortisol secretion early in the morning, which continuously decreases during the day (Edwards, Clow, Evans, & Hucklebridge, 2001; Kirschbaum & Hellhammer, 1989). However, there are also ultradiurnal variations within cycles of one hour (de Kloet, 2014). This needs to be considered in study procedures, i.e. testing should be in the afternoon, when cortisol levels can be expected to be relatively low. Otherwise, if baseline receptor occupation is already high due to the morning peak levels of endogenous cortisol, one can hardly study the effects of receptor *activation*.

When cortisol binds to the MR in the brain, it gives rise to quite a number of different observable effects depending on the receptors location in the brain and on the exact timing of measurement. In behavioral experiments, rapid *non-genomic effects* have been distinguished from much slower *genomic effects* (de Kloet, 2014).

On a neurophysiological level, the rapid non-genomic effects are attributed to the so-called membrane-bound MR of the presynaptic cell membrane and are related to glutaminergic excitatory effects of synaptic neurotransmission (Joëls, de Kloet, & Karst, 2011; Joëls et al., 2008; Joëls, Pasricha, & Karst, 2013; Joëls et al., 2012; Khaksari, Rashidy-Pour, & Vafaei, 2007; Popoli, Yan, McEwen, & Sanacora, 2012; Schwabe, Schächinger, et al., 2010); especially by involving excitatory glutamate release in the prefrontal cortex and the hippocampus (Joëls et al., 2008; Popoli et al., 2012).

In contrast to the membrane-bound MR, the so-called nuclear MR translocates, i.e. moves, inside the cell nucleus to effect modulations in gene expression (Groeneweg et al., 2012; Meinel, Gekle, & Grossmann, 2014). Cortisol binding at the nuclear MR results in a conformational change in shape, thereby activating the receptor (Fuller, 2015). The activated nuclear MR acts as a transcription factor of gene expression via modulation of mRNA production. Some MR regulated genes have already been identified, but a clear picture of the genes that are targeted by the effects of cortisol, as a ligand binding to the genomic MR, still needs further research (Fuller, 2015). Because of the broad variety of biological functions modulated by cortisol ranging from the stress response, emotion regulation and metabolic

processes to immunology, it is hypothesized that a great number of genes are affected (Joëls et al., 2012). Figure 2 illustrates the postulated different neurophysiological mechanisms of nuclear and membrane-bound MR.

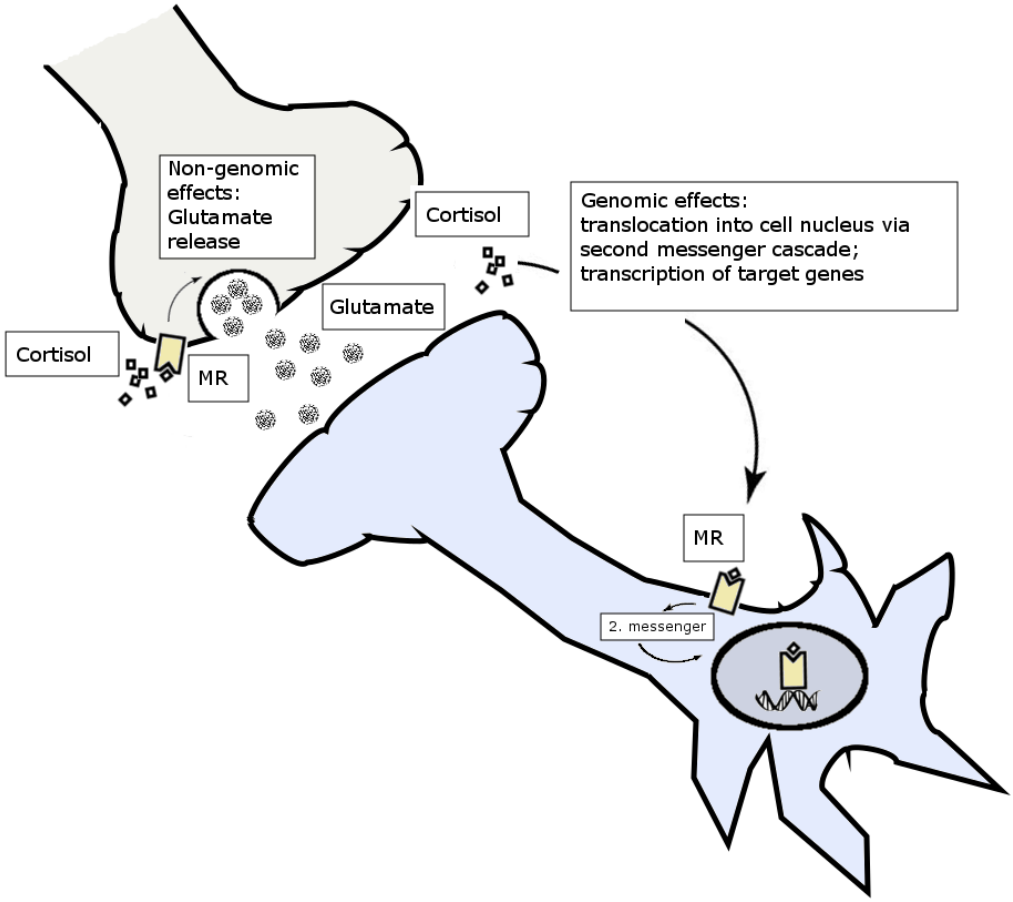

Figure 2. Schematic characterization of the assumed neurophysiological underpinnings of membrane-bound non-genomic vs. nuclear genomic MR effects according to Popoli et al. (2012).

Previously, the MR was understudied, because it was assumed that its high affinity to cortisol leads to a permanent occupation of the nuclear MR even at the circadian nadir (Vogel, Fernández, Joëls, & Schwabe, 2016). However, the membrane-bound MR has a lower affinity to cortisol, similar to the affinity of the GR, and is activated at high cortisol levels as seen e.g. during stress-exposure (Joëls et al., 2008; Karst et al., 2005). Through this discovery, research has recently started to pay closer attention to the MR, especially with regard to the role of the membrane-bound MR during the stress-response and its role in cognitive functioning.

Stress-related acute peaks in cortisol release follow a specific course over time. After stress-exposure, cortisol levels peak from about 15 to 30 minutes after stress exposure and return to the baseline levels after approximately one hour to 90 minutes (de Kloet, 2014; de Kloet et al., 2005). Immediately after stress-exposure, the non-genomic effects are activated within seconds to minutes and last until the cortisol level declines again (Groeneweg et al., 2012; Karst, Berger, Erdmann, Schütz, & Joëls, 2010; Karst et al., 2005). On the contrary, the genomic effects of MR occupation take several minutes to hours (de Kloet, 2014). Figure 3 illustrates the time-dependent effects of nuclear MR and GR as well as membrane-bound MR and its association with the cortisol level.

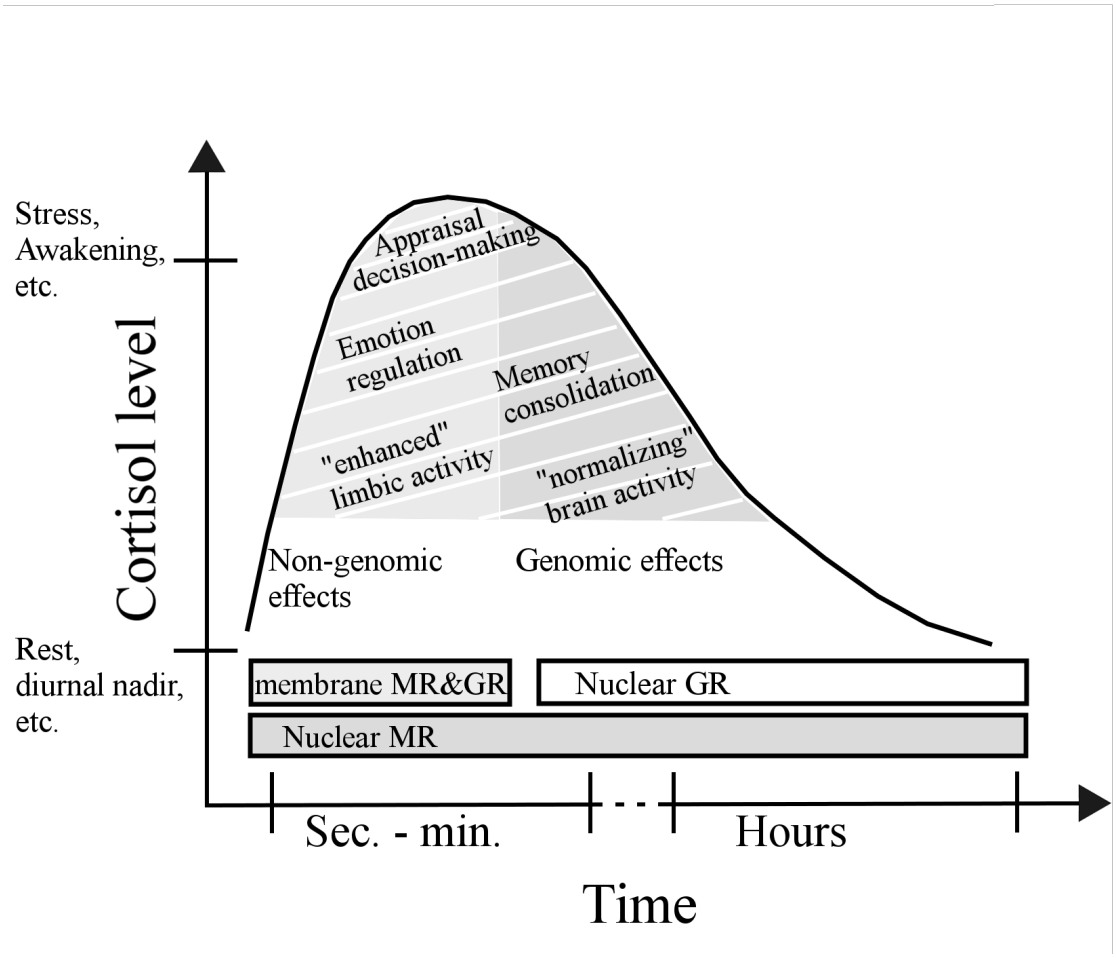

Figure 3. This schematic model represents the underlying mechanisms of the time-dependent effects of MR and GR occupation with cortisol. In the early phase, emotional processes are enhanced, promoting the adequate appraisal of the stressful situation, whereas in the later phase, cognition and memory consolidation for future reuse is improved. This figure is a modified and extended illustration based on figure 6 in de Kloet (2014).

Studies have shown that memory formation is improved through the genomic effects of nuclear MR and that retrieval of long-term memory is impaired via the non-genomic effects of membrane MR during acute stress (Ter Heegde et al., 2015). Therefore, it is already established that the MR is decisive for an optimal appraisal and memory formation during stressful situations, which is biologically consistent with the high expression of the MR in the limbic system; a brain area particularly important for processing incoming sensory information, memory and selecting learning strategies (Ter Heegde et al., 2015).

In sum, increasing evidence indicates that the non-genomic effects of the membrane-bound MR are important for the appraisal in urgently stressful situations (Joëls et al., 2008). In comparison, the genomic effects of the nuclear MR are important for maintaining the viability and responsiveness to the environment and reset the threshold of the stress response (Ter Heegde et al., 2015).

However, the exact contribution of membrane-bound MR as opposed to nuclear MR or GR is still somehow unclear. It is often assumed that for some cognitive functions MR and GR work together in a complementary fashion, whereas for others they work independently or even mediate opposing actions (de Kloet, 2014).

One goal of this dissertation project is to help disentangle the role of the MR for these complex time-dependent interactions of cortisol receptors in the brain (see section 2). Prior to this, the following sections give a short overview about what is already known from animal studies and initial evidence in humans with regard to the role of the MR on cognitive function (section 1.3.3), mood (section 1.3.4), and social cognition (section 1.3.5).

1.3.3 The MR and cognitive functioning

Several animal studies examined the role of MR blockage on cognitive function by inactivating the MR gene in mice (NR3C2-KO mice). For instance, mice with a lack of limbic MR-expression exhibit deficits in working memory (Berger et al., 2006), spatial memory (Berger et al., 2006; V Brinks, Berger, Gass, De Kloet, & Oitzl, 2009; S. Qiu et al., 2010; J. Ter Horst, Van Der Mark, et al., 2012), and spatial learning (J. Ter Horst, Van Der Mark, et al., 2012; J. P. Ter Horst et al., 2013). Furthermore, studies have

shown that a MR antagonist can affect strategies of spatial learning in reply to novelty (Oitzl & De Kloet, 1992; Oitzl, Fluttert, & Ron de Kloet, 1994).

In humans, MR blockage with spironolactone impairs cognitive performance in selective attention, visuospatial memory and executive function (Otte et al., 2007). Moreover, MR blockage has detrimental effects on selective attention as measured by using the d2 test[8] under non-stressful conditions and working as well as long-term memory after stress-exposure (Cornelisse, Joëls, & Smeets, 2011). MR-blockage with spironolactone also leads to an impairment of memory retrieval in particular with regard to emotional material (Rimmele, Besedovsky, Lange, & Born, 2013) and abolishes the stress-induced enhancement of inhibitory control in the stop-signal task in healthy participants (Schwabe, Höffken, Tegenthoff, & Wolf, 2013). In addition, MR-blockage with spironolactone inhibits the stress-induced shift from hippocampus-dependent declarative memory towards striatum-dependent procedural learning (Schwabe, Tegenthoff, et al., 2013) and thereby impairs performance in classification tasks significantly (Schwabe, Tegenthoff, et al., 2013).

Moreover, there are a number of preclinical studies that investigate the role of MR stimulation in mice with genetic MR overexpression showing enhanced spatial memory (Lai et al., 2007) and improved non-spatial memory consolidation and memory processes (Ferguson & Sapolsky, 2008; Harris, Holmes, De Kloet, Chapman, & Seckl, 2013; Rozeboom, Akil, & Seasholtz, 2007).

Human studies that used the potent MR agonist fludrocortisone found enhanced cognitive performance both in prefrontal cortex-associated and hippocampus-associated cognitive domains in elderly as well as young healthy participants (Hinkelmann et al., 2014), and in depressed patients as well as healthy participants (Otte et al., 2015). Furthermore, Groch, Wilhelm, Lange, and Born (2013) found an improved consolidation of declarative memory after fludrocortisone administration. Moreover, Wingenfeld et al. (2015) found improved working memory after fludrocortisone administration in healthy women. Dorey et al. (2011) have shown that the MR, but not the GR, mediates the rapid and non-genomic effects of stress and mediates memory retrieval.

[8] The d2 test measures attention and is sometimes also known as cancellation task (Brickenkamp, Schmidt-Atzert, Liepmann, & Schmidt-Atzert, 2010)

In sum, both animal and humans studies confirm that MR *stimulation* has beneficial effects, whereas MR *blockage* has detrimental effects on cognitive performance in both hippocampus-dependent as well as prefrontal cortex dependent cognitive domains.

1.3.4 The MR and mood

Besides the just presented findings on MR and cognition, there are only few studies that examined the impact of the MR on mood.

Several preclinical studies found that the intake of antidepressive medications leads to an up-regulation of the MR. These very interesting findings were especially true for the hippocampus (Barden, Reul, & Holsboer, 1995; Brady, Whitfield Jr, Fox, Gold, & Herkenham, 1991; Reul, Stec, Söder, & Holsboer, 1993; Seckl & Fink, 1992; J. Yau, Olsson, Morris, Meaney, & Seckl, 1995; J. L. Yau, Hibberd, Noble, & Seckl, 2002).

Due to these results it is promising to examine, whether MR stimulation has beneficial effects in depressive patients, since these patients are characterized through decreased MR expression (de Kloet et al., 2016; Klok et al., 2011; Medina et al., 2013). This was already examined in humans by using the antidepressant escitalopram and additionally the very potent MR agonist fludrocortisone to stimulate the MR (Otte et al., 2010). Otte et al. (2010) found a faster response after the additional intake of the MR agonist in patients with depression. These results confirm the beneficial effects of the MR, not only for cognition in depressed patients, but also for mood.

There are several studies that found concurring results. For instance, Plihal, Krug, Pietrowsky, Fehm, and Born (1996) found that a stimulation of mainly the MR results in a change towards positive mood.

In contrast to this beneficial effect of fludrocortisone as e.g. an add-on to antidepressive medication, there are several studies, which examined the influence of the MR antagonist spironolactone on bulimia, premenstrual syndrome and bipolar disorder. Regarding the influence of spironolactone on bipolar disorder, the authors of a case study with 4 patients found reduced residual symptoms after the intake of spironolactone as add-on to the usual medication (Juruena, Gama, Berk, & Belmonte-de-Abreu, 2009). Moreover O'Brien, Craven, Selby, and Symonds (1979) and M. Wang,

Hammarbäck, Lindhe, and Bäckström (1995) found beneficial effects of spironolactone administration on premenstrual syndrome. Furthermore, Wernze (1999) found that the intake of spironolactone influenced eating behavior and mood in patients with bulimia.

Taken together, there is evidence that the MR influences mood in healthy participants and patients with psychiatric disorders. However, due to the heterogeneous findings, it still remains unclear whether MR stimulation (e.g. fludrocortisone) or rather MR blockage (e.g. spironolactone) leads to better mood.

1.3.5 The MR and social cognition

Despite the fact that humans have to cope with stressful situations in their everyday life and interaction with others, the role of MR and stress in relation to social cognition remains surprisingly understudied. Nevertheless, since the effects of MR on classical memory tasks are well explored, recent studies have begun to investigate more complex paradigms and more specific aspects of human cognition.

Social cognition is important for communication, interaction (Beer & Ochsner, 2006) and emotional competence. In stressful situations, aspects of social cognition such as facial emotion recognition can become challenging. However, the ability to recognize emotions from, e.g. facial expressions is of pre-eminent importance, particularly in stressful situations, which are closely related to emotions like fear, but also delight, and ordained emotions can for themselves evoke stress (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). The stress-induced activation of the HPA-axis leading to a boost in plasma cortisol levels, may also lead to alterations in social cognition (Sandi & Haller, 2015). Furthermore, as mentioned before the lateral septum and the amygdala, where the MR is highly distributed (de Kloet, 2014), are associated with effective stress coping (Singewald et al., 2011) and with emotion (Rolls, 2015; Sheehan et al., 2004).

Nonetheless, very little is known about the specific role of cortisol on social cognition such as emotion recognition and even less is known about the influence of the MR on social cognition. Smeets, Dziobek, and Wolf (2009) showed that stress impairs social cognition and influences empathy. Takahashi et al. (2004) found impaired social memory after psychosocial stress (Trier social stress test). Moreover,

Deckers et al. (2015) found better recognition of faces after psychosocial stress (Trier social stress test). These results were found in patients with borderline personality disorder and also in healthy participants. Furthermore, there are only few studies, which focused on the influence of cortisol on selective attention (attentional bias) after emotional priming (MacLeod, Mathews, & Tata, 1986), and these studies yield divergent results (Hakamata et al., 2013; McHugh, Behar, Gutner, Geem, & Otto, 2010; Putman, Hermans, Koppeschaar, Van Schijndel, & Van Honk, 2007; Putman, Hermans, & van Honk, 2010; Roelofs, Bakvis, Hermans, van Pelt, & van Honk, 2007; Tsumura & Shimada, 2012; van Honk et al., 1998). Some of these studies found hints, that cortisol increased the selective attention to negative stimuli (Putman & Roelofs, 2011; Roelofs et al., 2007; Tsumura & Shimada, 2012; van Honk et al., 1998, 2000), especially in the early phase after psychosocial stress induction (Roelofs et al., 2007; Tsumura & Shimada, 2012). These diverse results could be explained by differences in cortisol levels, the intake of exogenous cortisol or psychological stress, the manner of elicitation, the material of stimuli, and the length of stimulus presentation.

More specifically, there are only few studies that directly investigated the role of MR stimulation or blockage on aspects of social cognition. An overview of these studies is summarized below.

Preclinical studies that examine the influence of MR inactivation found that the MR plays an important role in emotional arousal, fear, contextual fear memory and coping strategies (V Brinks et al., 2009; Zhou, Kindt, Joëls, & Krugers, 2011). Furthermore, Zhou et al. (2011) found, that the MR is crucial for the recall of emotional material and for fear response selection. J. Ter Horst, Carobrez, Van Der Mark, De Kloet, and Oitzl (2012) found that inactivating the MR gene impaired regulation of behavioral flexibility that transcends the adaptation in adverse situations, including the extinction of fear-motivated behavior. J. P. Ter Horst et al. (2014) examined how the depletion of the MR influences social discrimination and found detrimental effects on the ability of social discrimination, however, only in male but not in female mice. Moreover, studies that examined animals with genetic MR overexpression found reduced anxiety in rodents (Lai et al., 2007; Mitra, Ferguson, & Sapolsky, 2009; Rozeboom et al., 2007).

Studies on humans, which blocked the MR by using the potent MR antagonist spironolactone, found that the blockage had detrimental effects on the retrieval of

emotional material (Rimmele et al., 2013). These results could be confirmed by MR blockage with metyprapone (Rimmele, Besedovsky, Lange, & Born, 2015). Furthermore, Wingenfeld et al. (2014) investigated the influence of the MR agonist fludrocortisone on empathy and found that patients with borderline personality disorder and healthy women show better emotional empathy after fludrocortisone intake than after placebo intake. This improvement of empathy was not found regarding cognitive empathy.

Moreover, it has been shown that a MR gene (NR3C2) polymorphism (rs5522) moderates the amygdala reactivity in participants that experienced childhood emotional neglect (Bogdan, Williamson, & Hariri, 2012). Moreover, variants of the MR gene is associated with higher optimism in women with depression (Klok et al., 2011) as well as with a memory bias for negative emotions (Vogel et al., 2014).

In short, there is evidence that the MR plays an important role in aspects of social cognition, like in emotional empathy and emotional memory. Moreover, there is evidence that the MR is important for the perception and behavioral integration of the ability to react in unfamiliar situations (de Kloet et al., 1999) and for the regulation of behavioral flexibility that transcends the adaptation in adverse situations (J. Ter Horst, Carobrez, et al., 2012).

1.3.6 The MR in patients with Addison's disease

In 1855, Thomas Addison discovered a disease, which was characterized by hyperpigmentation and symptoms of wasting (phthisis). As a result of these symptoms he described a malfunction of the adrenal gland (Addison, 1855). Years later this disease was called primary adrenal insufficiency or Addison's disease. It is a life-threatening disease, which is characterized by a lack of endogenous cortisol and aldosterone production, i.e. by a hypocortisolism and a hypoaldonsteronism, which leads to a reactively higher ACTH and CRH release (Arlt & Allolio, 2003; Quinkler, 2012). Figure 4 presents the activity of the HPA-axis in patients with Addison's disease compared to healthy participants.

The etiology of Addison's disease is very heterogeneous, e.g. autoimmune adrenalitis, genetic disorders, thrombosis, operation or medication (Arlt & Allolio, 2003; Quinkler, 2012). It takes on average very long time to diagnose Addison's

disease correctly and it is easily misdiagnosed due to its unspecific symptoms like weight loss, lack of energy, fatigue and weakness, malaise, low blood pressure and dehydration (Arlt & Allolio, 2003; Quinkler, 2012). Frequent misdiagnoses are, e.g., depression, anorexia nervosa, irritable bowel syndrome or chronic enteritis (Quinkler, 2012).

Addison's disease is very rare. The prevalence is 100 to 140 per million (Quinkler, 2012). It peaks in the fourth decade of life, and women have a higher risk than men for developing the disease (Arlt & Allolio, 2003).

Adequate replacement therapy for cortisol and aldosterone is essential for survival in Addison's disease and was developed in 1949 (Arlt & Allolio, 2003). The life-long hormonal replacement therapy is realized by using the potent GR agonist hydrocortisone and the potent MR agonist fludrocortisone (Arlt & Allolio, 2003; Quinkler, 2012). The conventional dosage of hydrocortisone ranges between 15 to 25 mg per day and the conventional dosage of fludrocortisone ranges between 0.05 to 0.2 mg per day (Arlt & Allolio, 2003; Quinkler, 2012).

Without replacement therapy the risk of getting an adrenal crisis is high, especially after stress exposure, like psychological stress, infections or fever (Quinkler, 2012). In such stressful situations, a heightened cortisol level is physiologically needed. Due to the pathologically low endogenous cortisol levels in Addison's disease, stress can therefore result in a cardiovascular collapse and death (Quinkler, 2012).

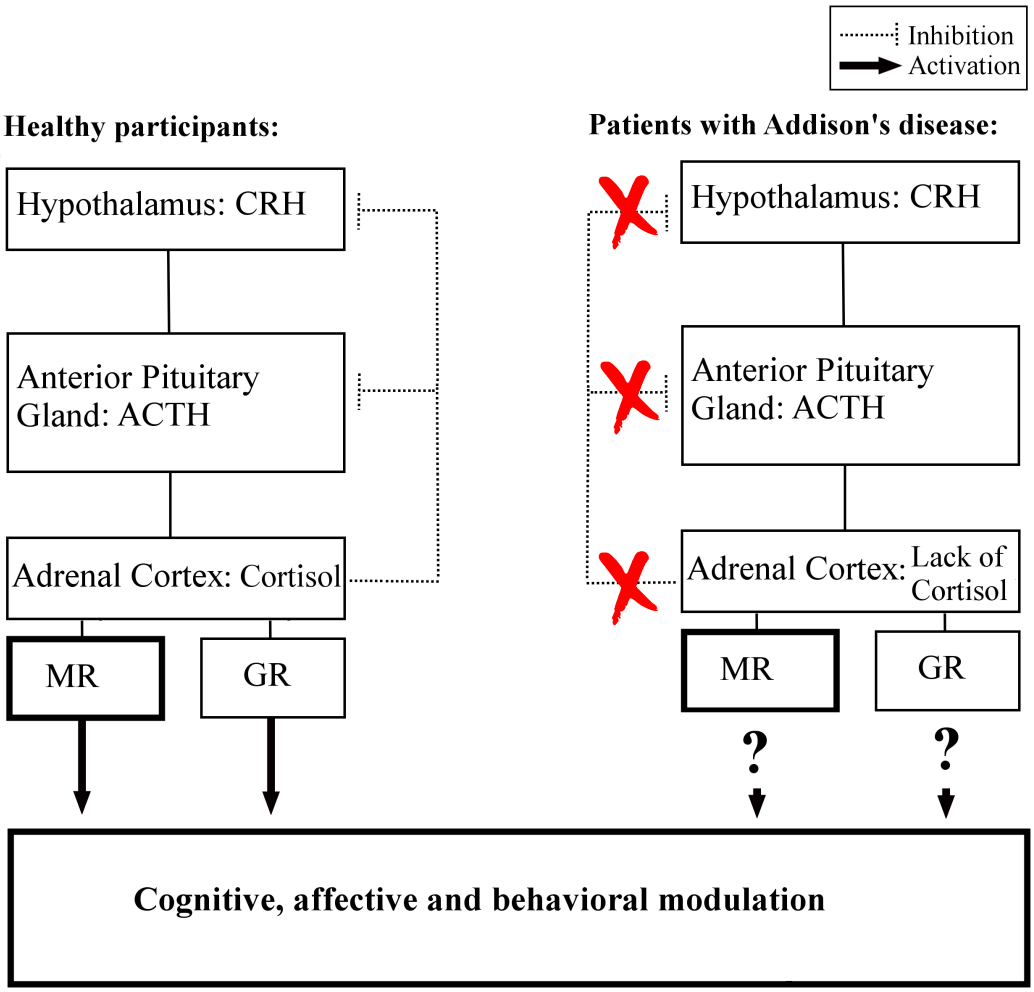

Figure 4. HPA-axis activity in healthy participants and patients with Addison's disease. The left side represents the normal HPA-axis activity with the release of cortisol that results in a negative feedback on the HPA-axis. The right side visualizes the pathology: due to insufficient cortisol release, the negative feedback on the hypothalamus and the anterior pituitary is lacking, which leads to a reactively heightened CRH and ACTH production.

In spite of hormone substitution, quality of life is severely impaired in patients with Addison's disease, and cognitive functioning as well as mood contributes essentially to quality of life (Bleicken et al., 2008; Bleicken, Hahner, Loeffler, et al., 2010; Hahner et al., 2007; Kluger et al., 2014; Løvås et al., 2010; Løvås, Husebye, Holsten, & Bjorvatn, 2003; Løvås, Loge, & Husebye, 2002).

Since the GR and the MR play an important role in cognitive function and in mood (de Kloet, 2014; section 1.3.3 & 1.34) it is worthwhile to examine these domains in patients with Addison's disease. Interestingly, only few studies examined cognitive functioning in patients with Addison's disease. These studies found that the

patients show worse performance in prefrontal cortex-dependent cognitive domains like attention (Klement et al., 2010; Klement et al., 2009) and in hippocampus-dependent domains like episodic memory (Henry & Thomas, 2014). However, these studies are methodologically limited (Schultebraucks, Wingenfeld, Heimes, Quinkler, & Otte, 2015) and a methodologically improved investigation using well established neuropsychological test batteries as well as adequate power is required.

More specifically, there is only one study with nine Addison patients (and no control group) that examined cognitive functioning in these patients as a function of GR and MR occupation (Tytherleigh, Vedhara, & Lightman, 2004). This study indicated that the MR may play a crucial role for hippocampus-dependent cognitive performance like the encoding of learned material (Tytherleigh et al., 2004).

In sum, only little is known about cognitive functioning in patients with Addison's disease and about the effects of long-term hormone replacement therapy on cognitive performance in these patients. Especially the implicated role of the MR requires further meticulous examination.

1.3.7 Pharmacokinetics and pharmacodynamics of fludrocortisone

Taken together, the information provided in the preceding sections points out that the MR plays an essential role for cognitive function, mood and social cognition as well as for patients with Addison's disease. As outlined in section 1.2, one reasonable approach to investigate such outcome variables as a function of MR occupation is to acutely stimulate the receptor with the potent MR agonist fludrocortisone. Fludrocortisone is a synthetic form of cortisol with highly improved mineralocorticoid properties and is regularly used as part of the medication regimen of patients with Addison's disease.

In the three studies of this dissertation, we used Astonin H® and Florinef®, which are both fludrocortisone acetate. The pharmacokinetic and -dynamic properties of fludrocortisone are complex, but important for the research rationale. Fludrocortisone acetate is quickly dissolved in human plasma by hydrolysis and its uptake is virtually complete (Quinkler, Oelkers, Remde, & Allolio, 2015). About 20 minutes after oral intake, fludrocortisone can be detected in the blood and reaches peak levels after 90 to 120 minutes after intake (Quinkler et al., 2015). Studies

described half-lives of the elimination from the blood in two phases (2-4 h and 4-6 h) or three phases (2-3 h, 4.5 and 10.2 h), resulting in fludrocortisone levels below 20% after 16 hours (Quinkler et al., 2015). This time frame has been taken into account in this dissertation (further information regarding the time frame can be found in Schultebraucks, Deuter, et al. (2016); Schultebraucks et al. (2015); (Schultebraucks, Wingenfeld, Otte, & Quinkler, 2016)).

The chemical structure of fludrocortisone is very similar to that of cortisol (hydrocortisone). In fact, the only difference is an extra fluorine atom in position 9α, therefore, fludrocortisone is also called 9α-fluorohydrocortisone.

Cortisol and fludrocortisone have a similar affinity[9] to both the MR and the GR with a preference to the nuclear MR by a factor of ten (see table 1). The affinity of cortisol to the membrane-bound MR is very similar to and in the range of its affinity to the nuclear GR (Karst et al., 2005). A specific affinity of fludrocortisone to the membrane-bound MR has not yet been reported in the literature.

Table 1. Relative affinity of cortisol and fludrocortisone to the MR and the GR

	Cortisol	Fludrocortisone	References
Nuclear GR affinity	1[a]	1[b]	[a]de Kloet (2014); Wyrwoll et al. (2011)
Nuclear MR affinity	10[a]	15[b]	[b]Agarwal, Coupry, and Philippe (1977)
Membrane-bound MR affinity	0,5 – 1[c]	?	[c]Karst et al. (2005)

Although the affinity of both fludrocortisone and cortisol to the nuclear MR is very similar (Oelkers et al., 1994), fludrocortisone is about 125 to 3000 times more potent than cortisol (see table 2). The potency of an agonist like cortisol or fludrocortisone depends on several factors like receptor affinity but also on receptor number or drug concentration and is tissue-specific (e.g. kidney vs. hippocampal neurons) as well as

[9] Pharmacologically, it is important to distinguish between affinity and potency of an agonist and a corresponding receptor. The affinity of an agonist is a measure of how strong it binds to a receptor. Potency refers to the amount needed to produce a certain effect like e.g. salt retention (MR) or immunosuppression (GR).

effect-specific (e.g. salt retention vs. cognition). This explains in part the broad range of the MR potency of fludrocortisone reported in the literature.[10] The fact that fludrocortisone is more potent to activate the MR than cortisol can be explained by the slight difference in chemical structure (Axelrod, 2001).[11]

Table 2. Summary of the relative MR and GR potency of cortisol and fludrocortisone

	Cortisol	Fludrocortisone	References
GR potency (*genomic effects* – e.g. anti-inflammatory, immunosuppressant and metabolic effects)	1[a] 1[b] 1[c]	11[a] 12[b] – [c]	[a]D. Miller, Brueggemeier, and Dalton (2008) [b]Melmed, Polonsky, Larsen, and Kronenberg (2015) [c] Karow and Lang-Roth (2016)
MR potency (*genomic effects* – e.g. sodium and water retention and potassium depletion effects)	2[a], 1[b], 1[c]	125[b], 300-800[a], 3000[c]	

To sum up, fludrocortisone has a very high potency to activate the MR in the human brain. However, due to its limited but existing GR potency, it should be kept in mind that high dosages of fludrocortisone could also result in some GR co-activation in addition to MR activation. Nonetheless, fludrocortisone is a well-describe potent MR agonist and is the state-of-the-art method to examine the effects of MR stimulation in the human brain.

[10] A further complication is whether *in vivo* or *in vitro* methods were used to quantify potency or whether rodent or human tissue was examined. Therefore, it is currently difficult to state the exact MR potency of fludrocortisone for the here-examined effects with regard to cognitive function, mood and social cognition.

[11] Given the extra fluorine atom, fludrocortisone is *not*, but cortisol *is* rapidly oxidized into cortisone by the 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) enzyme (Oelkers et al., 1994) and cortisone is unable to activate the MR (Oelkers et al., 1994). Furthermore, CBG has also a high affinity for cortisol, but not for fludrocortisone (Wyrwoll et al., 2011). Therefore, both CBG and 11β-HSD2 also prevent cortisol, but not fludrocortisone, to bind to its receptors. In spite of the very similar MR affinity of cortisol and fludrocortisone (see table 1), the much higher MR potency of fludrocortisone compared to cortisol (see table 2) may therefore be explained by the different affinities to 11β-HSD2 and CBG.

2 Aims and design of the Dissertation Project

The main objective of this dissertation project is to examine human MR function and its role for behavior modulation, cognition, mood and social cognition; as pointed out above, all aspects that are still underexplored and constitute a research gap. In order to shed light on these psychoneuroendocrinological interactions, the effects of high MR occupation in patients with Addison's disease as well as in healthy subjects are examined. Because of their pathophysiology with regard to MR and GR function, patients with Addison's disease are well suited to serve as a model for examining the role of MR and GR occupation in hippocampus-, prefrontal cortex- and amygdala-related neuropsychological domains.

The first study of the project examined how long-term cortisol substitution with the MR agonist fludrocortisone affects cognition in patients with Addison's disease (Schultebraucks et al., 2015). Complementary, the underlying paradigm of the second study was to explore how high MR occupation with the individually-adapted daily dose of fludrocortisone affects cognition and mood in patients with Addison's disease (Schultebraucks, Wingenfeld, et al., 2016). In addition, the third study of the project explored the fludrocortisone-induced effects of high MR stimulation in limbic structures of healthy subjects with regard to social cognition (Schultebraucks, Deuter, et al., 2016).

2.1 Research questions and hypotheses

In the next sections, the specific research question of each study is explicated and corresponding hypothesis are formulated. Afterwards, the rational of the three studies will be presented to illustrate how each study was designed in order to address the specified research question and to test the corresponding hypotheses.

2.1.1 Study I: Cognitive function in patients with Addison's disease

As presented in section (1.3.6), patients with Addison's disease lack adequate levels of physiologically produced cortisol and aldosterone. Without replacement therapy, the disease can lead to death. Several studies have examined the role of hormone replacement therapy on quality of life and they found detrimental effects in spite of hormone substitution. Besides quality of life, there is still only scarce knowledge concerning the long-term effects of hormone substitution in Addison's disease with regard to neuropsychological functions. Due to this research gap the following research question was formulated.

Research question:

Does long-term hormone substitution with hydrocortisone and fludrocortisone affect cognitive function in Addison's disease?

Hypothesis:

Since natural endogenous cortisol release is a fine-tuned complex and time-dependent matter of circadian and ultradiurnal rhythmicity as well as context-sensitive demands (section 1), and further, since hormone replacement is rather context-insensitive, we hypothesized that long-term hormone substation will affect cognitive functioning. So that patients with Addison's disease will show worse cognitive function compared to age-, sex- and education matched healthy controls. Since hydrocortisone and fludrocortisone act via the GR and the MR, and since the highest expression of these receptors is in the hippocampus, it was hypothesized that hippocampus-dependent cognitive deficits will be especially pronounced.

2.1.2 Study II: The role of the MR in patients with Addison's disease

Preclinical and human studies have shown that the MR has an important impact on cognitive functioning (section 1.3.3). It is therefore interesting to examine whether cognitive performance is a function of MR occupation in patients with Addison's disease, who lack endogenous cortisol and aldosterone. Because there is initial

evidence that the MR also influences mood (section 1.3.4), the question arises what role the MR plays with regard to these aspects.

Research question:

How does the MR affect cognitive function and mood in Addison's disease?

Hypothesis:

In line with previous empirical findings it was hypothesized that the MR will influence both cognitive functioning and mood in patients with Addison's disease; i.e. the patients with Addison's disease will show better cognitive performance and better mood under conditions of high MR occupation (i.e. after fludrocortisone intake) than without fludrocortisone intake (low MR occupation).

2.1.3 Study III: MR stimulation and social cognition in healthy participants

Although there is evidence that the MR influences cognitive functioning in healthy participants, as well as in patients with psychiatric disorders like depression and also in patients with Addison's disease, there are only few studies that examined the role of the MR on more complex cognitive domains, such as social cognition (section 1.3.5). It is already known that stress influences selective attention and it can be assumed that a fast orientation of attention to potential threats is adaptive and evolutionary plausible.

Since the literature describes an attentional bias toward stimuli of negative valence in the early phase of the stress response, where the membrane-bound MR plays a decisive role, it is very interesting to examine the influence of selective MR stimulation on selective attention. Furthermore, since Wingenfeld et al. (2014) found an enhanced emotional empathy after fludrocortisone administration, and since emotion recognition is important for empathy, it is also very promising to examine the role of MR stimulation on emotion recognition as well.

Research question:

What is the role of MR stimulation in aspects of social cognition like selective attention and emotion recognition? What influences do potential sex-differences exert on social cognition after MR stimulation?

Hypothesis:

In accordance with research stressing the role of MR for the "fight", "fright" or "flight" behavioral adaptation (section 1.3.2), it was hypothesized that high MR occupation via stimulation with fludrocortisone will lead to an attentional shift towards negative stimuli and to an improvement of emotion recognition in facial expressions.

2.2 Rationale of the three studies

In the following the rational of the three studies will be briefly outlined. Thereby, it is intended to provide an explanation of how the studies were designed to extend the already existing knowledge (section 1) to answer the derived research questions (section 2.1).

The first and second study were conducted in cooperation with the Department of Psychiatry and Psychotherapy at the Charité – Universitätsmedizin Berlin, CBF and the Department of Endocrinology at the Charité – Universtitäsmedizin Berlin, CCM. These two studies were approved by the ethics committee of the Charité – Universitätsmedizin Berlin. All of the participants provided their written informed consent.

The third study was realized in the Department of Psychiatry and Psychotherapy of the Charité – Universitätsmedizin Berlin, CBF. This study was approved by the ethics committee of the German Psychology Association (DGPs). All of the participants provided their written informed consent.

2.2.1 Participant recruitment

Marcus Quinkler, who was working in the outpatient clinic at Charité Mitte provided invaluable help to recruit the patients with Addison's disease. Since Addison's disease is a very rare disease, it took seven months to recruit and test the 30 patients with Addison's disease and the 30 age-, sex- and education-matched controls. The healthy controls were recruited via postings in universities, public spaces and websites. All participants received an expense allowance of 50 Euro. The inclusion and exclusion criteria were clearly stated (see the specific studies). The drop-out rate was zero, every patient, who came to the first appointment, has also come to the second appointment.

In the third study, young female and male students were recruited via postings on websites and notices in universities. The testing of the 40 female and 40 male participants lasted for seven months. The expense allowance was 40 Euro. The inclusion and exclusion criteria were clearly stated (see the specific study). The drop-out rate was a single case and due to technical problems with the computer required for testing.

In all of the three studies, the Structured Clinical Interview for DSM-IV (SKID-I) was conducted to ascertain whether the participants had a previous or acute psychiatric disorder, which was an exclusion criterion. In all of the three studies, there were several participants who did not meet the inclusion criteria in the screening and could not participate in the testing.

Since fludrocortisone interacts with contraceptives and since the endogenous sex hormone progesterone binds as an antagonist at the human MR (Rupprecht et al., 1993), it was important to balance female and male participants in the third study and to balance the number of female participants who took oral contraceptives in the placebo and the fludrocortisone group (McEwen, de Kloet, & Wallach, 1976).

2.2.2 Randomization process

In both studies, the randomization was done by employing the online computer program "research randomizer" (Urbaniak & Plous, 2013). A randomization list was

created so that the treatment allocation was concealed and the group assignment of participants could not be predicted (see the specific studies).

2.2.3 Blinding

The first and second study were single-blinded, i.e. the examiner did not know whether the patient with Addison's disease took fludrocortisone two hours before testing or after testing. Due to ethical reasons, the study was not designed double-blinded, given that hormone substitution in these patients is essential for survival. However, the outcomes were assessed blinded to the participants' group assignments. Also the analysis of data was always blinded to group membership. Further information is given in the specific studies (Schultebraucks, Deuter, et al., 2016; Schultebraucks et al., 2015; Schultebraucks, Wingenfeld, et al., 2016).

The third study was double-blind and placebo-controlled, i.e. neither the examiner, nor the participants knew, whether participants have taken 0.4 mg fludrocortisone or a placebo. Statistical analysis of the data was also blinded to group membership.

2.2.4 Treatment selection

In order to achieve high MR occupation in patients with Addison's disease, their usual individually-adapted daily dose of fludrocortisone was administered before testing, whereas in the condition of low MR occupation, the patients with Addison's disease received their respective daily dose (mean: 0.1 mg) after testing. In the third study 0.4 mg fludrocortisone was used to acutely stimulate the MR, because of it's pharmacokinetic and pharmacodynamics properties that have been characterized above (section 1.3.7).

Although fludrocortisone may have some GR potency, it is the best-suited pharmacological agent to activate the MR because it has a manifold higher affinity for the MR than for the GR. Therefore, the dosages of fludrocortisone used in our studies are very likely to result in high MR occupation in the brain and probably in only marginal co-activation of the GR (Otte et al., 2015). This is also supported by the

assumption that 0.4 to 0.5 mg fludrocortisone per day is the recommended maximal dose for adults and that only above this threshold of 0.4 to 0.5 mg per day, glucocorticoid effects of fludrocortisone are to be expected (Karow & Lang-Roth, 2016).

In all of the three studies, testing took place two hours after fludrocortisone acetate (Astonin H® or Florinef®) intake to reach optimal MR occupation, which takes place approximately 90 to 120 minutes after digestion (section 1.3.7). The dosage of 0.4 mg (maximal dosage for adults) could be used, since in the third study, only yound and healthy participants were tested with normal body mass index. Further information concerning treatment selection can be found in (Schultebraucks, Deuter, et al., 2016; Schultebraucks et al., 2015; Schultebraucks, Wingenfeld, et al., 2016).

2.2.5 Measurement of blood pressure

Blood pressure was controlled, because hypertension affects cognition (Gifford et al., 2013) and fludrocortisone is known to be vasopressor. Therefore, the measurement of blood pressure was important in all of the three studies in order to control for potential confounding variables.

2.2.6 Measurement of salivary cortisol

In the first and second study, no salivary cortisol was measured, because patients with Addison's disease have no endogenous cortisol (section 1.3.6). In the third study, salivary cortisol samples were collected five times (prior, during and after testing) to monitor the cortisol response after fludrocortisone and placebo intake.

Due to the circadian rhythm of cortisol release (section 1.3.2), all testings took place in the afternoon. Even if patients with Addison's disease have no endogenous cortisol, it was nonetheless important to conduct the testing in the afternoon, since the matched healthy controls were to be measured at the same time of day and for them it was important to avoid circadian peaks in endogenous cortisol secretion.

Because it is well known that the MR antagonist spironolactone increases HPA activity (Heuser, Deuschle, Weber, Stalla, & Holsboer, 2000), it was hypothesized that fludrocortisone would lower the salivary cortisol level over time by virtue of its negative feedback on HPA activity. This inhibitory effects of fludrocortisone has already been established in several studies (Buckley, Mullen, & Schatzberg, 2007; Karamouzis et al., 2013; Otte et al., 2003) and was used as indirect treatment check for the fludrocortisone-induced MR activation.

2.2.7 Selection of the psychological tests

Since the aim of the first and second study was to examine how long-term hormone replacement therapy influences cognitive performance in patients with Addison's disease compared to healthy controls and to examine the influence of MR occupation on cognitive performance (section 2.1.1 and 2.1.2), it was necessary to chose a well-established neuropsychological test battery that encompassed several cognitive domains, like verbal memory (Auditory verbal learning test), visual-spatial memory (Rey–Osterrieth complex figure test), working memory (Digit Span task), executive function (Stroop test), attention (Number-Combination test) and autobiographical memory (Autobiographical memory test). The specific cognitive tests were explained in detail in the respective studies.

To assess the acute psychological state, i.e. mood, composure-restlessness and vigilance-fatigue, the MDBF (Mehrdimensionaler Befindlichkeitsfragebogen) was used and for depressive symptoms, the PHQ-9. In the third study we used the emotional dot-probe to measure selective attention and the facial emotion recognition task.

After having introduced the rationale of this dissertation, the three studies of the present dissertation will now be presented.

3 Cognitive function in patients with Addison's disease (study I)

Cognitive function in patients with primary adrenal insufficiency (Addison's disease)

This chapter was published as

Schultebraucks, K., Wingenfeld, K., Heimes, J., Quinkler, M., & Otte, C. (2015). Cognitive function in patients with primary adrenal insufficiency (Addison's disease). *Psychoneuroendocrinology*, *55*, 1-7.

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4 The role of the MR in patients with Addison's disease (study II)

The Role of Fludrocortisone in Cognition and Mood in Patients with Primary Adrenal Insufficiency (Addison's Disease)

This chapter was published as

Schultebraucks, K., Wingenfeld, K., Otte, C., & Quinkler, M. (2016). The Role of Fludrocortisone in Cognition and Mood in Patients with Primary Adrenal Insufficiency (Addison's Disease). *Neuroendocrinology*. 103(3-4), 315-320. DOI: 10.1159/000438791

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5 MR stimulation and social cognition in healthy participants (study III)

Selective attention to emotional cues and emotion recognition in healthy subjects: the role of mineralocorticoid receptor stimulation

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This chapter was published as

Schultebraucks, K., Deuter, C. E., Duesenberg, M., Schulze, L., Hellmann-Regen, J., Domke, A., Lockenvitz, L., Kuehl, L. K., Otte, C. & Wingenfeld, K. (2016). Selective attention to emotional cues and emotion recognition in healthy subjects: the role of mineralocorticoid receptor stimulation. *Psychopharmacology*. *233*(18), 3405-3415. DOI: 10.1007/s00213-016-4380-0

https://dx.doi.org/10.1007/s00213-016-4380-0

6 General discussion

The research questions examined in the three studies of the present dissertation project were designed to help answer the question: What is the role of the MR on cognitive function, mood and social cognition? Each study had a different focus and approach. In the following discussion, the results of these studies will be summarized and discussed.

First, on a behavioral level, the particular results concerning cognitive function (section 6.1.1), mood (section 6.1.2) and social cognition (section 6.1.3) are briefly reviewed and discussed in light of the existing body of literature. Second, the strengths and limitations of the studies are presented (section 6.2). Third, in section 6.3, the results are integrated into a general synthesis as well as into theoretical models of neuronal MR function; namely the MR/GR balance hypothesis on the molecular level of corticosteroids (section 6.3.1) and the "salience network" on the level of functional brain connectivity (section 6.3.2). A promising hypothetical mechanism underlying these models of MR function is the facilitation of glutamatergic neurotransmission as well as the rapid regulation of synaptic plasticity (section 6.3.3).

Subsequently, the implications for future research on MR functioning will be presented and promising new hypotheses will be derived as well as potential interventions briefly discussed (section 6.3.4). Finally, the conclusion of the dissertation summarizes the key points and encapsulates the main findings from behavioral, functional and cellular levels into a unified picture of the MR (section 6.4).

6.1 Discussion of the main findings

As pointed out at the very beginning (section 1), the MR plays an important role for the appraisal of stress-related situations and the selection of adequate response strategies (de Kloet, 2014). Dysfunction, blockade or underexpression of the MR can lead to cognitive and emotional alterations (section 1.3.3 & 1.3.4). The aim of this dissertation was to further examine the role of MR functioning on cognitive function, mood and social cognition. Since Addison's disease is characterized by a lack of glucocorticoids (cortisol) and mineralocorticoids (aldosterone), this disease provides

a unique possibility to examine the clinical effects of MR and GR occupation. Recent research on Addison's disease has mainly focused on effects of glucocorticoids and DHEA replacement on patient's well-being, whereas the effects of MR replacement have received very little attention.

To recall, the first aim was to investigate the impact of long-term hormone-substitution with fludrocortisone and hydrocortisone on cognitive functioning in Addison's disease (study I). The second aim was to examine how the MR influences cognitive functioning and mood in these patients (study II). Finally, the third goal was to investigate the role of MR on social cognition in healthy subjects (study III).

6.1.1 The MR and cognitive functioning in patients with Addison's disease

Previous studies have shown that MR stimulation improves, whereas MR blockage impairs cognitive performance in hippocampus- and prefrontal-cortex-dependent domains (section 1.3.3). However, it remained unclear from these studies how long-term hormone substitution with fludrocortisone and hydrocortisone that act via the MR and GR affects cognitive functioning. It remained also unclear whether high as opposed to low MR occupation is beneficial for cognitive functioning in patients with Addison's disease.

Contrary to our hypothesis, we found that patients with Addison's disease show no clinically significant differences in cognitive performance compared to carefully matched controls, except in verbal learning (Schultebraucks et al., 2015). These results are remarkable since these patients had already been treated with long-term hormone substitution using hydrocortisone and fludrocortisone for about eighteen years (SD = 11), which did not lead to broad cognitive impairment in our sample (Schultebraucks et al., 2015). Although the patients reported subjective concentration problems, these deficits could not be objectified in this study; notwithstanding a well-established neuropsychological test battery was used (Schultebraucks et al., 2015).

These results fit very well to other studies that examined cognitive performance in patients with Addison's disease (Henry & Thomas, 2014; Klement et al., 2010; Klement et al., 2009). Moreover, our results have been directly confirmed by a subsequent study that also found only slight cognitive deficits in patients with

Addison's disease (Tiemensma, Andela, Biermasz, Romijn, & Pereira, 2016). Their results can be seen as further support for the here presented results.

Moreover, we found that systolic blood pressure in patients with Addison's disease correlates with performance in hippocampus-dependent cognitive domains, i.e. the higher the systolic blood pressure, the worse the performance in the hippocampus-related cognitive domains (Schultebraucks et al., 2015). These effects are well known in healthy participants (Gifford et al., 2013), but have not been reported in patients with Addison's disease before.

Given the cognitive deficits in hippocampus-dependent domains found in the first study (verbal learning), it was worthwhile to further examine the role of MR occupation on cognitive functioning in these patients in a second study.

In line with our hypothesis, we found better cognitive functioning (verbal memory, and on a trend level in attention and executive function) after fludrocortisone intake (high MR occupation) than without fludrocortisone intake (low MR occupation). These effects were already found after skipping the regular individually adapted daily dose of fludrocortisone (mean: 0.1 mg ± 0.3 mg) just once (Schultebraucks, Wingenfeld, et al., 2016).

These results extend studies on MR functioning in healthy men, demonstrating that blocking the MR diminishes memory performance, cognitive flexibility and attention (Otte et al., 2007; Rimmele et al., 2013), as well as studies showing that MR blockage impairs working memory and selective attention after psychosocial stress-induction (Cornelisse et al., 2011).

In addition, studies in humans showed beneficial effects of MR stimulation on visual-spatial memory, working memory and short-term memory (Hinkelmann et al., 2014), as well as verbal memory and executive function (Otte et al., 2015) and on consolidation of declarative memory (Groch et al., 2013). However, these results are heterogeneous, since Wingenfeld et al. (2015) found no significant influence of fludrocortisone on verbal or visual-spatial memory, but an improvement in working memory in healthy women. Nevertheless, the results of the second study that high MR occupation is beneficial for hippocampus-dependent cognitive functions like verbal memory and prefrontal cortex-dependent functions like attention and executive function (Schultebraucks, Wingenfeld, et al., 2016) fit nicely to an increasing body of literature on MR function in both animals and humans.

The slight cognitive impairments of patients with Addison's disease compared to healthy controls along with more depressive symptoms and decreased systolic blood pressure (Schultebraucks et al. 2015) might result from maladjustment of the HPA-axis as a consequence of the long-term substitution therapy with fludrocortisone and hydrocortisone. This may result in an imbalance of MR and GR, since the replacement therapy is not flexibly enough adjusted to the varying and spontaneous situational requirements (de Kloet et al., 1999). This is in line with the results of Tytherleigh et al. (2004) who found that for memory processing, a balanced activation of MR and GR is indispensable. They found significant differences in verbal learning, which is biologically plausible, since verbal learning is related to the hippocampus, where the MR and GR are highly expressed (de Kloet, 2014).

Moreover, de Kloet et al. (1998) found that long lasting hypocortisolism after an adrenalectomy in rats results in hippocampal loss of synaptic function and neurodegeneration. This highlights the importance of how long the hypocortisolism went unnoticed before hormone substitution therapy started. The elapsed time prior to adequate hormone substitution and any associated potential neurodegeneration could be another explanation for the mild cognitive impairments found in Addison's patients.

A further explanation could be that replacement therapy with hydrocortisone resulted in elevated cortisol levels, which was recently found in Addison's disease by hair cortisol analysis (Staufenbiel et al., 2015). That elevated cortisol levels influences cognitive functioning is well studied in patients with Cushing Syndrome, which is characterized by excess of cortisol. However, in contradistinction to the only marginal cognitive deficits in patients with Addison's disease, studies have shown major cognitive deficits in patients with Cushing Syndrome and these deficits remain even after cure (Crespo et al., 2014; Forget, Lacroix, Bourdeau, & Cohen, 2016; Forget, Lacroix, Somma, & Cohen, 2000; Martignoni et al., 1992; Michaud, Forget, & Cohen, 2009; Resmini et al., 2011; Tiemensma et al., 2010). Either way, adequate replacement therapy for cognitive function in Addison's disease hinges critically on mineralocorticoid and glucocorticoid steroid as well as receptor balance.

In section 6.3.1 to 6.3.3 a hypothetical mechanism of MR-mediated changes in a synaptic transmission and plasticity is proposed that makes it biological plausible

how different MR to GR ratios in brain networks involving e.g. hippocampus, amygdala and prefrontal cortex can lead to the found rapid behavioral effects.

To sum up, our findings shed light on the long-term effects of Addison's disease and the required hormone replacement therapy on cognitive functions in these patients. Due to their high clinical importance for the treatment of Addison's disease, these results are reassuring, showing that the long-term replacement with fludrocortisone and hydrocortisone does not impair cognitive performance in a broad and severe manner. Our results further corroborate the assumption that an adequate MR occupation is indispensable for optimal cognitive functioning. In addition, our results confirm the hypothesis that MR occupation has an influence on hippocampus- and prefrontocortical related cognitive domains as well as in subjects lacking endogenous cortisol and aldosterone.

6.1.2 The MR and mood in Addison's disease

Previous studies presented very heterogeneous and partly inconsistent results with regard to the question whether, and especially how, the MR influences mood (section 1.3.4). In the first study (Schultebraucks et al., 2015), patients with Addison's disease reported significantly more depressive symptoms than the control group after long-term hormone substitution via the MR and the GR agonists fludrocortisone and hydrocortisone. Furthermore, patients reported significantly worse mood, more fatigue and restlessness compared to the control group (Schultebraucks et al., 2015). The well-described diminished quality of life in patients with Addison's disease (Bleicken et al., 2008; Bleicken, Hahner, Loeffler, et al., 2010; Hahner et al., 2007; Kluger et al., 2014; Løvås et al., 2010; Løvås et al., 2003; Løvås et al., 2002) was therefore confirmed by the patients' subjective reports in our study (Schultebraucks et al., 2015).

In the second study, patients with Addison's disease showed better mood after high MR occupation compared to low MR occupation (Schultebraucks, Wingenfeld, et al., 2016). Intriguingly, vigilance/fatigue and composure/restlessness were not influenced by MR occupation. The beneficial influence of high MR occupation on mood fits very well to findings of Plihal et al. (1996) who reported better mood after MR stimulation. Moreover, Otte et al. (2007) found beneficial influence of

fludrocortisone as an add-on to antidepressant medication and an examination of the inhibitory negative feedback of cortisol on the HPA axis in depressed patients and healthy controls indicates impaired MR function in depression (Hinkelmann et al., 2016).

Finally, blocking the MR with spironolactone in healthy young men lead to increased negative mood in non-stressful conditions (Vogel et al., 2015). This mimics our finding that patients with Addison's disease reported worse mood after skipping fludrocortisone intake (Schultebraucks, Wingenfeld, et al., 2016), which leads to decreased MR occupation in these patients similar to the seen effect of MR blockade in healthy young men (Vogel et al., 2015).

These MR effects on mood can be well integrated into the MR/GR balance hypothesis (section 6.3.1) and a theoretical model of MR-mediated presynaptic glutamate release as well as the so-called neuroplasticity hypothesis of mood disorders that crucially involves the non-genomic MR effects (section 6.3.3).

In sum, we could confirm the results of previous studies showing that, despite hormone substitution, quality of life is impaired in patients with Addison's disease. Moreover, we could show that mood is influenced by MR occupation in these patients, namely high MR occupation is beneficial for mood in Addison's disease.

6.1.3 The MR and social cognition

The MR plays a crucial role for appraisal-processes and in the selection of response strategies to potentially stressful situations like „fight", „flight" or „fright" (section 1.3.5). Since the MR turned out to have an important impact on cognitive functioning and mood in study one and two, it was very interesting to further investigate the role of the MR on more complex domains like social cognition; in particular on emotion recognition and selective attention.

In line with our hypothesis we found a shift in selective attention after fludrocortisone intake towards negatively valenced facial stimuli, and an attentional bias away from sad faces after placebo intake. We found no attentional bias towards happy faces; neither after fludrocortisone intake, nor after placebo intake.

With regard to selective attention, our results fit very well to findings of Tsumura and Shimada (2012) and Roelofs et al. (2007) who found an increased

attentional bias towards negative emotional stimuli in the early phase of stress response, where the non-genomic MR effects are present (section 1.3.2). Given the time frame between fludrocortisone administration and testing as well as the time frame of the pharmacokinetic properties of fludrocortisone uptake (section 1.3.7), it is likely that our findings of MR stimulation on selective attention are due to the non-genomic effects of the MR.

With regard to emotion recognition, we found – in contrast to our hypothesis – no significant effects of MR stimulation (Schultebraucks, Deuter, et al., 2016). Intriguingly, Deckers et al. (2015) found a significantly better emotion recognition after psychosocial stress induction. However, psychosocial stress activates both, the HPA axis and the noradrenergic system. Since neither Duesenberg et al. (2016) found a direct influence of the GR on emotion recognition nor we found a respective effect of the MR (Schultebraucks, Deuter, et al., 2016), it is indispensable to also examine the influence of the noradrenergic system on emotion recognition.

In sum, we found a shift in selective attention towards sad faces after 0.4 mg fludrocortisone intake in healthy subjects, indicating the relevance of acute MR stimulation for quick emotional processing of negative valence. However, we found no influence of MR stimulation on the capacity to recognize emotions in these healthy participants. These results present new information about the association between MR functioning and social cognition, especially to quick and automatic behavioral adaption towards emotional cues (selective attention).

This finding fits well to the recently postulated MR-mediated switch between "executive control network" to the "salience network" that seems evolutionary adaptive as a quick, automatic reaction to potentially stressful situations (section 6.3.2).

6.2 Strengths and limitations of the studies

This section outlines the strengths and weaknesses of each of the three blinded, randomized, matched, or placebo-controlled studies that were conducted in this dissertation project.

6.2.1 Strengths

The three studies have several strengths. First of all, clear inclusion and exclusion criteria were defined for all examined groups. In addition, treatment selection was carefully carried out on the basis of definite criteria extracted from previous evidence reported in the literature. Treatment effectiveness as well as patient safety guided treatment selection.

The patients with Addison's disease received adequate, individually adapted medical treatment. The mean daily dose of 21 mg of hydrocortisone in our sample is the average standard dose in state-of-the-art therapy in patients with Addison's disease (Husebye et al., 2014). The same is true for the 0,1 mg fludrocortisone dose (Quinkler et al., 2015). In the third study on social cognition, the dosage of 0,4 mg fludrocortisone was chosen.

Due to the fact that fludrocortisone has also some GR potency, a certain GR co-activation cannot be excluded. The affinity of fludrocortisone to the MR is 15 times higher than to the GR (Agarwal et al., 1977); although, more specifically, the affinity of membrane-bound hippocampal MR is likely to be in the range of the GR (Karst et al., 2005). With regard to the MR and GR potency of fludrocortisone, the literature is very scarce (section 1.3.7), but the threshold where GR effects are thought to occur from fludrocortisone intake, lies above dosages as high as 0,5 mg (Karow & Lang-Roth, 2016).[12] Therefore, our dosage of 0,4 mg was well suited to highly stimulate the MR, while still minimizing the risk of inadvertent GR co-activation and also corresponds to the dosage used in other studies (e.g. Hinkelmann et al., 2014; Otte et al., 2015). To reach full effectiveness, testing in all of the three studies, took place two hours after fludrocortisone intake when plasma concentration reaches its maximum (Ribot et al., 2013).

Moreover, the patients with Addison's disease were closely monitored regarding fludrocortisone therapy by measuring sodium and potassium levels, blood pressure and renin concentrations. The patients had normal sodium and potassium levels, normal blood pressure and renin concentrations at the upper limit of normal.

[12] This is of course only a rough estimation that is neither weight-adjusted nor specifically tailored to the here examined effects like cognition, mood or selective attention, but rather holds for the „classical" GR effects like metabolic and immunosuppressive effects (section 1.3.7).

This guaranteed that patients were treated correctly with fludrocortisone and there was no unintended side effect or adverse event in our sample. All participants of the three studies provided their written informed consent and all three studies were approved by the responsible ethics committees (section 2.2).

Furthermore, all of the three studies were either single-blind or double-blind, i.e. statistical analyses were performed blinded in all three studies and included, where adequate, post-hoc tests, Bonferroni correction and power analysis to support our findings. In addition, experienced clinical psychologists who were blinded to the treatment condition conducted the testing.

For the comparison of patients with Addison's disease and controls (study I), participants were systematically matched regarding to sex, age and education in the first study. Moreover, we also matched women with regard to their cycle phase. To control for potential confounding variables, variables that differed between both groups and that could influence cognitive functioning were used as covariates (body mass index, systolic blood pressure and depressive symptoms).

For comparison of patients with Addison's disease regarding high vs. low MR occupation (study II) as well as for the respective comparison of healthy subjects (study III), group allocation was randomized. Moreover, study III was placebo-controlled and participants were balanced with regard to sex.

Finally, in all of the three studies only well-established and validated methods were used for psychometric or neuropsychological assessment as well as for physiological measures like blood pressure and salivary cortisol analysis.

6.2.2 Limitations

To be sure, the three studies have some limitations. In study I and II, we recruited a rather small sample comprising 30 patients with Addison's disease and 30 healthy controls. This limitation should be seen in the context that it is challenging to recruit subjects with the very rare condition of Addison's disease (section 1.3.6). Statistical power was calculated and revealed sufficient power to detect moderate effects in the

first study.[13] In this study, we found no significant cognitive impairment in patients with Addison's disease, except for verbal learning. Given the insufficient power to detect small effects, we cannot exclude the possibility of slight impairments also in other cognitive domains besides verbal learning. In fact, Tiemensma et al. (2016) have replicated our results on verbal memory in an extended sample (n = 60) of patients with Addison's disease. In line with us, they found only mild cognitive impairments (Tiemensma et al., 2016).

In addition, also the second study was slightly underpowered; however, we had a moderate effect size that indicated a potential clinical significance of our results[14]. Nevertheless, one limitation is that more subtle differences may not have been detected, given the statistical power of the second study. In the third study, we examined a comparatively large sample with adequate statistical power to detect small effects. Moreover, the Bayes index[15] was calculated (Dienes, 2014) for the dissertation, to support our interpretation of the non-significant results in the emotional dot-probe and the facial emotion recognition task. The analysis of the

[13] For a priori sample size calculation, G*Power was used (Faul, Erdfelder, Buchner, & Lang, 2009). Since until now, no study compared patients with Addison´s disease with healthy controls with regard to cognitive performance, there was no prior information on what kind of effect sizes are to be expected. We therefore assumed a medium effect size of $f = 0.4$ for a priori sample size calculation. With $\alpha = 0.05$ and $1\text{-}\beta = 0.80$ a total sample of 52 was needed. In our study a total sample of 60 participants was tested and post-hoc power analysis revealed sufficient power (0.82) to detect at least moderate to large effects (partial eta square = .124), like for example in verbal learning.

[14] A priori sample size calculation was estimated using G*Power (Faul et al., 2009). Since no study systematically examined MR stimulation in patients with Addison's disease before, the expected effect size was estimated on the basis of a study in our research group that examined fludrocortisone effects in depressed patients (Otte et al., 2015). Given an effect size of $f = .30$ for verbal memory with $\alpha = 0.05$ and $1\text{-}\beta = 0.80$ a total sample of 24 was needed (ANOVA with repeated measurements). However, given the lack of comparisons between Addison patients and healthy controls, we conservatively assumed a smaller effect size of $f = 0.4$ for the comparison between Addison patients and healthy controls leading to a sample of $n = 26$ subjects in each group. To further conservatively allow for a discontinuation rate of $n = 4$ subjects in each group, we determined the necessary sample size to be $n = 30$ subjects in each group. Post-hoc power analysis revealed a power of 0.65 for a moderate effect (Cohen's $d_z = 0.38$) in the AVLT recall.

[15] The Bayes factor was calculated with JASP version 0.7.5.6. A Bayes factor <.33 indicates that the alternative hypothesis is correct and a Bayes factor > 3 indicate that the null hypothesis is correct, i.e. that there is no effect or no difference between groups (Dienes, 2014).

Bayes index (BF_{01}) revealed a BF_{01} = 4.29 for the attentional bias for happy faces and a BF_{01} = 7.45 for the main effect of drug in the facial emotion recognition task. This indicates in both cases that our interpretation of the results is correct; namely to adopt the null hypothesis that there are no respective group differences.

Besides the issues of statistical power, there are some further limitations of the studies. In the first and second study on cognition and mood in Addison's disease, we did not record the exact time of hydrocortisone intake. In consequence, it cannot be completely exclude that the intake of the mixed MR- and GR-agonist hydrocortisone showed a certain influence on the MR.

Finally, with regard to the third study on social cognition, the reliability of the emotional dot-probe task is sometimes questioned (Schmukle, 2005). This affects reliability of individual scores, but not of group differences in studies with an experimental treatment (Schmukle, 2005). In our study, we did not rely on a comparison of individual scores, but analyzed group differences. Therefore, the dot-probe paradigm of this study was sound and methodologically adequate.

6.3 Integration of the results

In light of the just outlined strengths and limitations of the studies, the presented results of each study give rise to a general synthesis of the dissertation project. Since we found that high MR occupation is beneficial for cognitive function and mood in patients with Addison's disease and since acute MR stimulation was associated with a significant shift in selective attention the following conclusion can be drawn:

The human MR plays an important role for cognitive function, mood and aspects of social cognition both in patient's lacking adequate MR occupation through endogenous cortisol as well as in healthy subjects. On the one hand high MR occupation is critical and beneficial for hippocampus- as well as prefrontal cortex-dependent cognitive function and mood in patients with primary adrenal insufficiency. On the other hand acute high MR occupation may influence automatic emotional processing, e.g., selective attention to sad faces, which may be functional in situations linked to physiologically high MR activation like during the initial phase of the stress response.

Figure 13 illustrates the results of this dissertation in a simplified way to highlight the main findings.

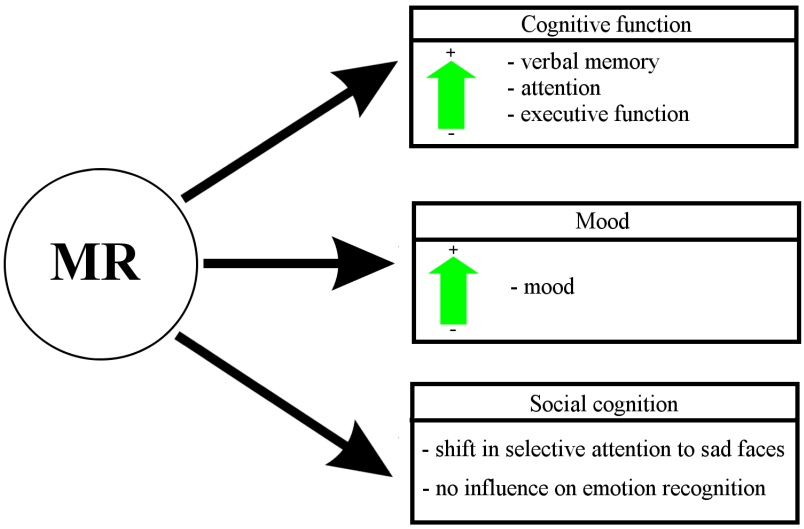

Figure 13. Summary of the main findings of the three studies comprised in this dissertation project.

The general synthesis of the dissertation fits well into theoretical models of MR function in the human brain, which emerge from the recent literature. First, on a molecular level, the so-called MR/GR balance hypothesis has long been established (section 1.2) and was recently extended by progress in the understanding of MR effects on neurotransmission and synaptic plasticity. Second, on a level of functional brain connectivity, an additional model postulates a shift of large-scale brain networks (Hermans, Henckens, Joëls, & Fernández, 2014) that is mediated by MR function (Vogel et al., 2016).

6.3.1 The MR/GR balance hypothesis and cognitive function and mood

On a molecular level and with regard to glucocorticoid equilibrium, the results of this dissertation confirm and extend the established MR/GR balance hypothesis in certain specific aspects. Quite generally, cortisol that binds to both, MR and GR, acts like a "double-edged sword" (de Kloet, 2014). Very high as well as very low cortisol levels can result in cognitive impairments (Het et al., 2005). Therefore, an optimal MR occupation is crucial for cognitive functioning and emotional processes. Previous studies have pointed out that cognitive function is improved by high MR occupation

and low to moderate GR occupation (de Kloet et al., 1999). These findings are extended by our results, which show that high MR occupation is beneficial for cognitive functions in patients with Addison's disease.

We found in patients with Addison's disease that, in addition to GR occupation through hydrocortisone, MR occupation through fludrocortisone was beneficial for cognition and mood (Schultebraucks, Wingenfeld, et al., 2016). These results corroborate the MR/GR balance hypothesis by showing that an MR to GR imbalance leads to specific emotional as well as cognitive alteration in patients with Addison's disease (Schultebraucks et al., 2015; Schultebraucks, Wingenfeld, et al., 2016).

More particularly, our results extend the MR/GR hypothesis by indicating that high MR occupation after fludrocortisone intake – and concomitant regular GR occupation via the usual daily dose of hydrocortisone – is beneficial for verbal memory, attention and executive function in patients with Addison's disease. Since imbalances of the MR to GR ratio may lead to deficits in these domains, an adequate adaptation to environmental challenges depends on optimal MR to GR balance.

These effects of the MR agonist fludrocortisone on hippocampus- and prefrontal cortex-related cognitive domains, fit well to the assumption that the membrane-bound MR is important for fast cognitive processing (Khaksari et al., 2007; Schwabe, Schächinger, et al., 2010) via glutamate release in the prefrontal cortex and hippocampus (Joëls et al., 2008; Popoli et al., 2012). The timeframe of the testing in our studies makes these non-genomic, membrane-bound MR effects likely to have taken place. Therefore, the beneficial effect of high MR occupation on cognitive function in patients with Addison's disease may be attributed to hippocampal or prefrontocortical non-genomic MR effects that help re-establish a functional balance between MR and GR. Similarly, the beneficial role of the MR on mood may also be attributed to non-genomic effects like glutamatergic neurotransmission (section 6.3.3)

On the basis of the so far available preclinical and clinical evidence, our results are thus also neurobiological plausible and fit to the hypothesis that "MR activation enhances excitability of limbic networks" (de Kloet, 2014, p. 2754). Recently, this assumption has been elaborated on the basis of meta-analyses on neuroimaging data, which analyze the role of large-scale brain networks as well as the underlying structural connectivity (Hermans et al., 2014). This endeavor gave rise to the

discovery of a so-called "salience network" that can also serve as a theoretical model to discuss the findings of this dissertation.

6.3.2 The salience network and the MR effects on selective attention

On a functional and structural level of brain circuitry, imaging studies revealed different large-scale brain networks like the "default mode network", the "executive control network" and the "salience network". These networks involve brain activity of several anatomically distinct brain regions that are linked by statistical correlation, i.e. functional connectivity as measured e.g. by functional Magnetic Resonance Imaging (fMRI), or linked by neuronal wiring and white matter tracts, i.e. structural connectivity as measured e.g. by structural or diffusion MRI (Z. Wang, Dai, Gong, Zhou, & He, 2015).

High MR occupation, as present in the initial phase of the stress response, was recently hypothesized to induce a quick shift from "cognitive" brain networks involving hippocampal and prefrontocortical structures to a non-cognitive automatic or "habit" network involving the amygdala and the dorsal striatum (Vogel et al., 2016). Moreover, in situations that are experienced as potentially unsafe or unknown, it is crucial to reallocate cortical resources in such ways as to orient attention to potential threats (Hermans et al., 2014). This is achieved by shifting from the "executive control network" to the "salience network", which results in a higher vigilance, more adequate appraisal and suppressed executive control (Hermans et al., 2014). The rapid, non-genomic MR effects seem to mediate this switch, since blocking the MR with spironolactone in healthy, young men prevented the stress-induced enhancement of functional connectivity of amygdala and dorsal striatum (Vogel et al., 2015).

Our results that the MR plays an important role in selective attention towards negative emotional cues concurs with the theoretical model of Hermans et al. (2014), who postulate that in the early phase of stress response the "salience network" is in play. This is complemented by the hypothesis that the MR mediates this shift via the rapid non-genomic effects of membrane-bound MR occupation that is also crucial in the initial stress phase (Vogel et al., 2016).

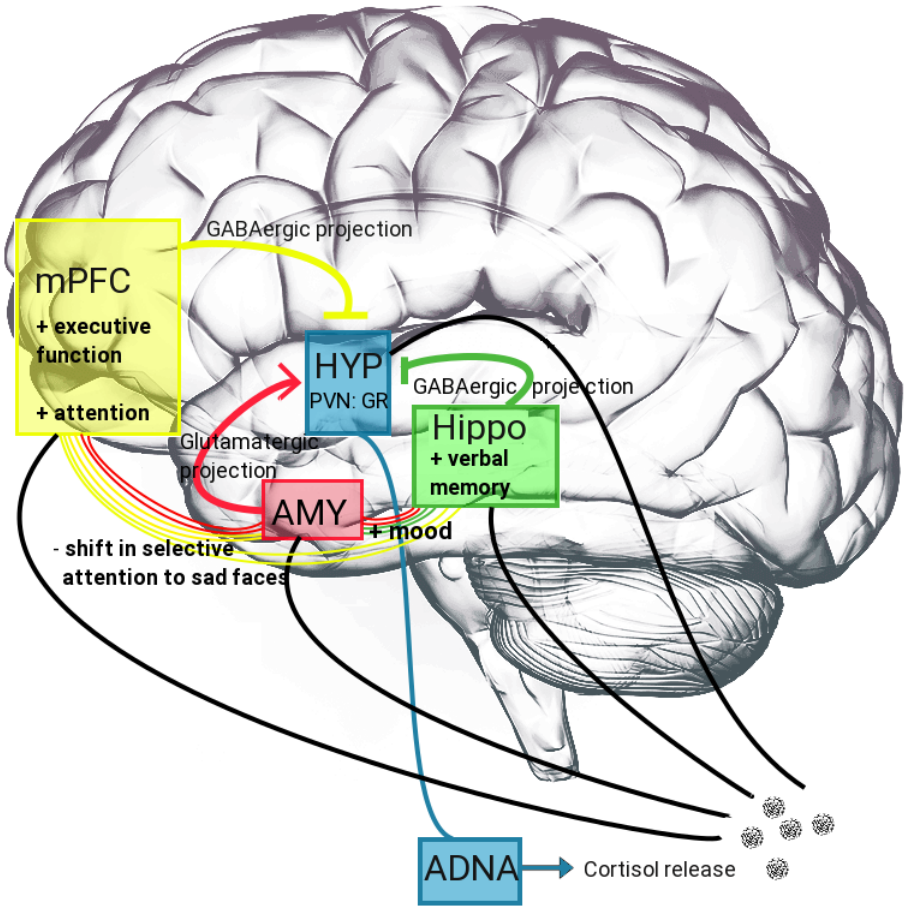

Figure 14. Schematic characterization of the limbic HPA-axis mediated by MR and GR. Cortisol release after acute stress induces a quick negative feedback on the HPA-axis via the non-genomic effects of MR and GR that inhibit the PVN through GABAergic projections from limbic structures.
Note: **ADNA**: adrenal gland, **HYP**: hypothalamus, **Hippo**: hippocampus, **mPFC**: medial prefrontal cortex, **PVN**: paraventricular nucleus

Furthermore, this MR-mediated shift towards "habit" network is compatible with the MR/GR balance hypothesis, which also points out that the non-genomic MR effects are important for the appraisal of unknown or potentially unsafe situations and the "fight", "fright" or "flight" response in the early phase of the stress reaction (de Kloet, 2014). In contrast, the "executive control network", which is important for higher-order cognition, is taking over only after stress has subsided and the emotional reactivity has been normalized (Hermans et al., 2014).

In sum, our results show that acute MR stimulation leads to a shift in selective attention towards negative emotional stimuli. Selective attention plays an important role for the adequate appraisal of new and potentially unsafe situations and for the

selection of appropriate response strategies. The shift of neural resources towards the salience network, involving less cognitive demanding response strategies, may explain this finding. In figure 14, a simplified schematic characterization is presented. On the one hand the non-genomic MR effects induced a shift away from prefrontal cortex and hippocampal cortical resources towards automatic habitual behavior like selective attention. This is seen after acute MR stimulation with 0.4 mg fludrocortisone in healthy subjects, which mimics the non-genomic effects of high MR occupation as seen in the physiological response to acute stressors (see figure 16). On the other hand the "normalization" of MR occupation as seen in the regular fludrocortisone replacement therapy in patients with Addison's disease (mean: 0.1 mg) does not reach these high levels of MR activation and corresponds rather to the physiological cortisol levels. This may explain the improvement of prefrontocortical and hippocampal cognitive domains and mood (see figure 14), which are already seen at much lower levels of MR occupation (see figure 16).

6.3.3 A hypothetical model of MR-mediated effects on neurotransmission and synaptic plasticity

The findings presented and discussed in this dissertation give rise to a hypothetical model of MR function implicated in cognitive function, mood and social cognition. A promising candidate for an underlying neurophysiological mechanism is the hypothesis that the MR mediates synaptic plasticity in the limbic system and facilitates glutamatergic neurotransmission in limbic glutamate pathways that project e.g. to the prefrontal, orbitofrontal and anterior cingulate cortex.

Although the cellular processes of the genomic and non-genomic MR effects are complex, an increasing number of preclinical and clinical evidence points to a crucial interplay between MR occupation and glutamatergic neurotransmission. Further elaborate research is certainly required to better understand the implicated neurophysiological details and one should be cautious; especially because the MR may also effect acetylcholine and monoamines like noradrenaline and serotonin via the endocannabinoid system (Joëls, de Kloet, et al., 2011). Therefore, membrane-bound MR action is highly complex (see figure 15).

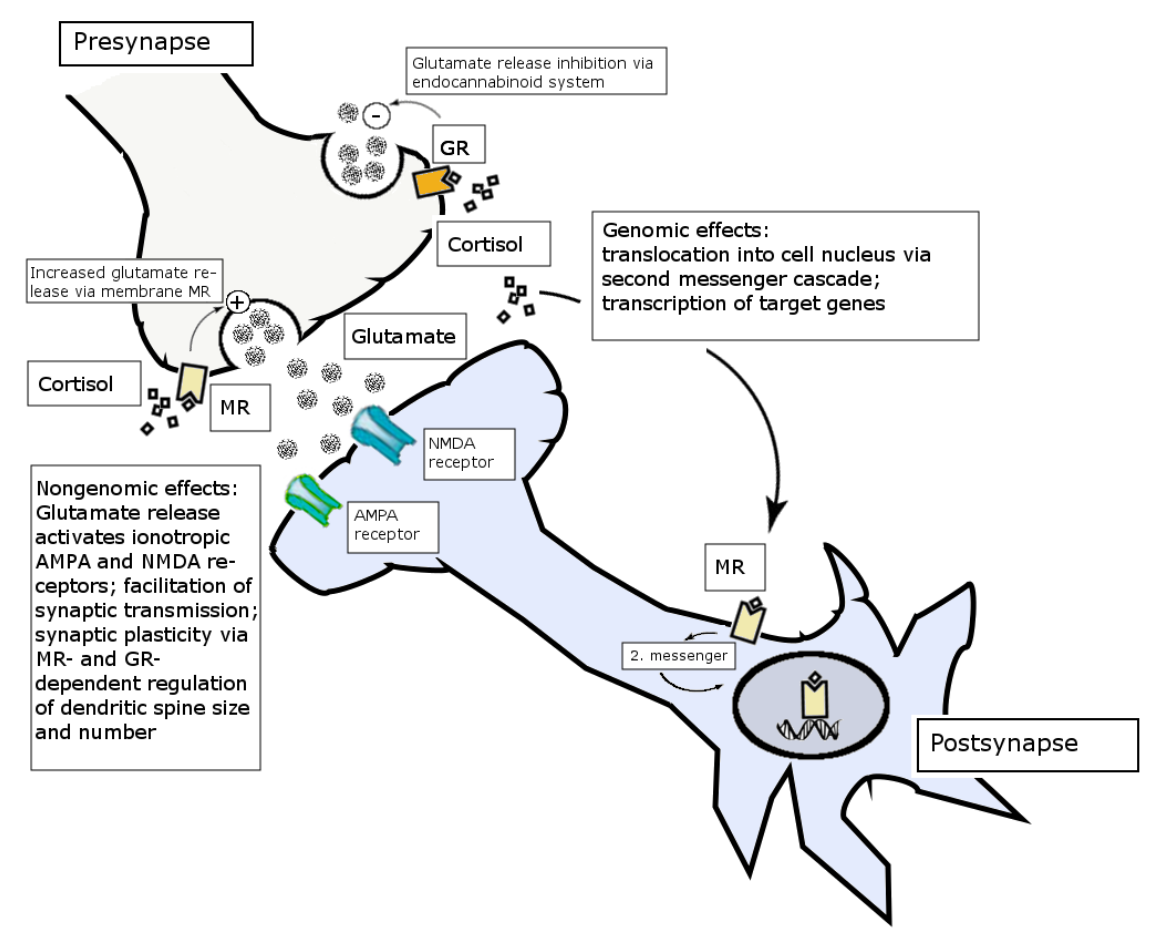

Figure 15. Simplified schematization of the mechanism of the MR-dependent glutamatergic neurotransmission based on Popoli et al. (2012).

Acute stress rapidly enhance the frequency of miniature excitatory currents at hippocampal and prefrontocortical synapses (Musazzi & Marrocco, 2016). Therefore, the rapid non-genomic effects have been linked to increase of glutamate release (Karst et al., 2005) through the activation of membrane-bound pre- and postsynaptic MR (Musazzi & Marrocco, 2016).

These rapid non-genomic MR effects are typically seen in acute stress (de Kloet et al., 2016) or after fludrocortisone administration. The presynaptically released glutamate acts on the postsynaptic NMDA and AMPA receptors and thereby facilitates glutamatergic neurotransmission (Popoli et al., 2012). Depending on the neuroanatomical target region – like the prefrontal cortex, the amygdala or the hippocampus – this MR-modulated glutamate release yields very diverse cognitive and affective effects (see figure 14). For example, also in the amygdala, cortisol rapidly results in neuronal plasticity by binding to MR and thereby facilitating

glutamate release (Karst et al., 2010). Synaptic plasticity and number of dendritic spines, which are continuously remodeled over time in dependence on novel experiences, learning and adaption to changing environments (Jeanneteau & Chao, 2013) seem therefore promising to yield novel insights into the underlying mechanism of stress-related neuropsychiatric disorders (Jeanneteau & Arango-Lievano, 2016).

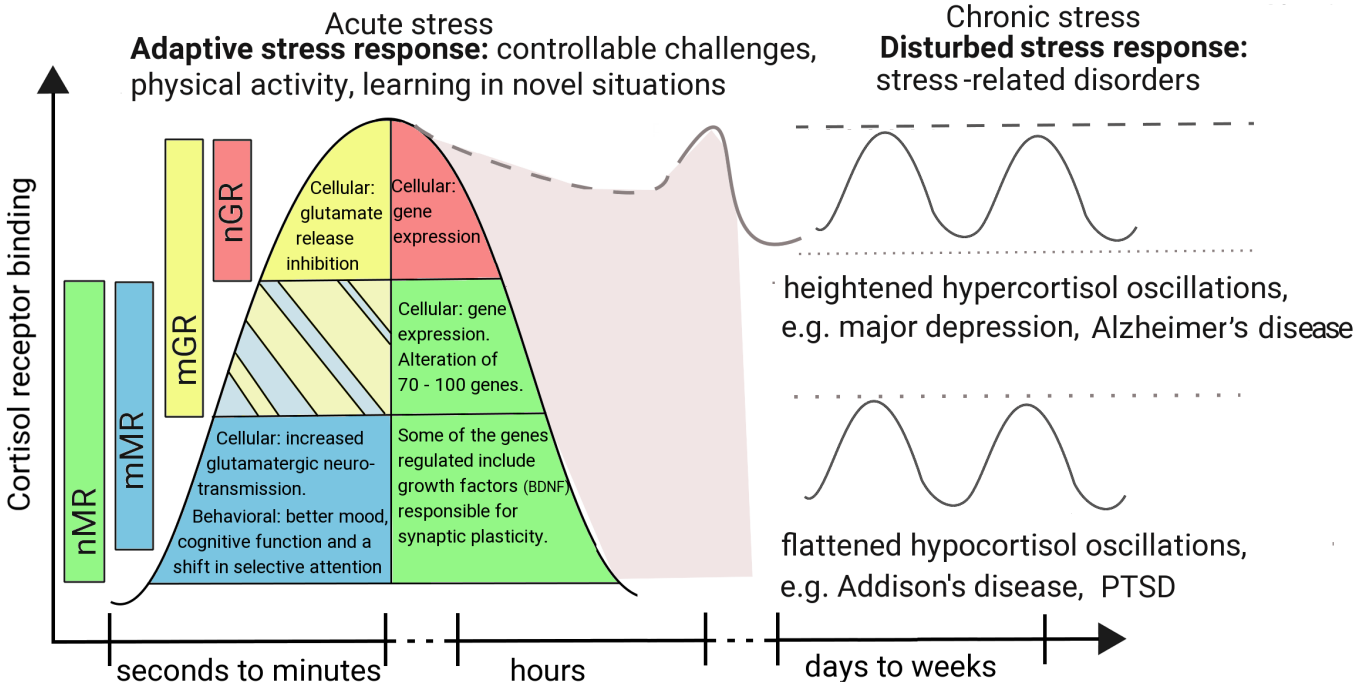

Figure 16. Hypothetical model of behavioral and cellular effects of cortisol receptor binding on membrane-bound (mMR) and nuclear (nMR) mineralocorticoid receptor as well membrane-bound (mGR) and nuclear (nGR) glucocorticoid receptor over the course of time.

Furthermore, the hippocampus and the prefrontal cortex rapidly inhibit the HPA axis through GABAergic projections to the PVN of the hypothalamus, whereas the amygdala plays an excitatory role via the glutamatergic pathways (Groeneweg, Karst, de Kloet, & Joëls, 2011; Herman, Ostrander, Mueller, & Figueiredo, 2005; McEwen, 1999). These feedbacks via GABAergic and glutamatergic projections to interneurons of the PVN can further modulate the release of CRH, ACTH and finally cortisol from the adrenal cortex (see figure 14).

This mechanism is not only useful to understand the findings of cognitive function in limbic structure-related domains, but is also implicated in mood disorders and the recently proposed glutamate hypothesis of depression (Sanacora, Treccani, & Popoli, 2012). This is plausible, since NMDA to AMPA ratio play a decisive role in mood disorders (Du et al., 2006) and since it is well known that chronic stress is linked to neuropsychiatric disorders like depression. In the long run, chronic stress leads to a down-regulation of MR in the hippocampus resulting in a low MR to GR ratio (de Kloet et al., 2016). In contrast, daily antidepressant intake increases MR expression after 5 weeks (de Kloet et al., 2016; López et al., 1998; Reul et al., 1993).

Furthermore, stress can also lead to neurodegeneration and neuronal atrophy in the hippocampus which has been linked to cognitive impairments and even Alzheimer's disease (Vyas et al., 2016). Taken together, there is a broad variety of domains ranging from cognitive function to social cognition and mood that are all to some extend regulated by the MR. The possible underlying mechanism may invariably be seen in the increased glutamatergic neurotransmission, which effects beneficial modulations of synaptic plasticity. Since, the MR is distributed in diverse anatomical structures ranging from prefrontal cortex to limbic structures, these diverse clinical effects may, with caution, be attributed to just one single mechanism: the modulation of glutamate release in diverse, but interconnected brain structures.

6.3.4 Implications for future research

The above-discussed findings (section 6.1.1, 6.1.2 & 6.1.3) entail several interesting research implications. For example, it seems important to examine in a longitudinal study in patients with Addison's disease, how cognitive function is affected by this disease and its progression over time.

Moreover, it is also interesting to examine the effects of fludrocortisone stimulation or lack thereof on neuropsychological domains in patients with Addison's disease, when replacement therapy is not only skipped once but more often. However, there are ethical reasons why we decided not to do so. In the end, Addison's disease is a severe condition that can even lead to death and requires adequate safety measures. Furthermore, it would also be very interesting to examine potential sex differences regarding cognitive functioning and mood in patients with Addison's

disease, since potential sex-dependent MR effects have been discussed (Ter Heegde et al., 2015).

With regard to social cognition, it seems promising to examine also the role of MR stimulation on other emotions like fear and anger and to see whether the found attentional shift after fludrocortisone is also linked to other "negative" stimuli or is specific to sad faces. Since our sample was restricted to very young and highly-educated healthy men and women it is important to extend these results to other samples of healthy participants as well as clinical samples, like patients with posttraumatic stress disorder (PTSD) or anxiety disorders. In major depression, which is characterized by heightened hypercortisol oscillations (see figure 16), it has already been demonstrated that MR blockade with spironolactone reduced cognitive empathy in patients with depression (Wingenfeld et al., 2016). By implication, it seems also promising to investigate whether MR stimulation, in contrast to MR blockade, has the opposite effect and is beneficial for cognitive empathy or other related domains of social cognition in major depression. In addition, it is interesting to examine whether fludrocortisone can have similar beneficial effects on cognition and mood in PTSD, which is similarly to Addison's disease characterized by flattened hypocortisol oscillations (see figure 16).

Moreover, studies have shown that facets of emotion processing, e.g. the reactivity of the amygdala after emotional neglect in the childhood, are moderated by genetic variances of the MR gene NR3C2 (Bogdan et al., 2012). Evidence shows that the haplotype 2 of the NR3C2 leads to higher optimism in women, which is linked to resilience for depression (Klok et al., 2011). Moreover, MR variances are associated with a memory bias with regard to negative emotions (Vogel et al., 2014). Thus, it would be interesting to investigate the differential influence of MR variances on affective processing. Since we found an attentional shift towards sad faces, it is particularly promising to examine the influence of the NR3C2 haplotype 2 on withdrawal-, social-, stress- and threat-related emotions like sadness, fear, anger or disgust; especially, to test for respective attentional biases (Schultebraucks, Deuter, et al., 2016). In sum, the examination of the differential role of genetic MR variances and to identify potential biomarkers is a promising field to proliferate the understanding of psychiatric disorders in relation to distorted HPA-axis-activity as a function of MR occupation in the brain.

In recent years, the MR has become a promising target of research on major depression (de Kloet et al., 2016; Hinkelmann et al., 2016; Otte et al., 2010; Otte et al., 2015). This is especially interesting in light of the so called glutamate hypothesis of depression (Sanacora et al., 2012) and the known facilitation of glutamatergic neurotransmission by MR stimulation (Popoli et al., 2012) that gave rise to investigations or glutamate agonists as rapid antidepressants (Abdallah et al., 2016; O. H. Miller, Moran, & Hall, 2016; Sanacora & Schatzberg, 2015; Zanos et al., 2016; Zorumski, Nagele, Mennerick, & Conway, 2015) or fludrocortisone as add-on treatment for major depression (Otte et al., 2010)

Similar to depression, cognitive decline is also characterized by a disturbed stress response of heightened cortisol levels as seen e.g. after chronic stress (see figure 16). Although still somewhat speculative, it was recently suggested to examine the role of the MR in neurodegenerative disorders like mild cognitive impairments (MCI) or Alzheimer's dementia (Gesmundo et al., 2016). An increasing amount of preclinical research indicates that GR antagonists like mifepristone may offer an promising therapeutic option in the future by restoring physiological cortisol levels and by reversing synaptic deficits and cell death in the hippocampus (Pineau et al., 2016). In particular, it has been shown in mice that long-term synaptic depression (LTD) selectively depends on impaired NMDA receptor transmission that is reversible under subchronic GR antagonist intake (Lante et al., 2015). Mifepristone reversed cognitive deficits as well as pathologically enhanced LTD present in the early symptomatic phase of the mouse model (Lante et al., 2015). The authors concluded that their data strongly argues "for a pathological synergistic interaction between chronic APP [read: amyloid precursor protein] misprocessing and HPA axis dysregulation." These beneficial effects were attributed to the GR antagonist, although it was conceded that "a role of MR cannot be excluded". Given the negative feedback of the MR on the HPA activity (figure 14), it seems plausible to also consider fludrocortisone as fruitful further target of symptomatic Alzheimer's disease research. All the more, since in rodents, fludrocortisone has already been shown to block the amyloid-β_{1-42}-induced "hyperphosphorylation of Tau protein, which is a main feature of Alzheimer's disease" (Gesmundo et al., 2016).

Taken together, one may derive the following hypothetical research question as desideratum: *Given the found beneficial effects of fludrocortisone on verbal memory*

in Addison's disease (Schultebraucks, Wingenfeld, et al., 2016), *can fludrocortisone be beneficial for the symptomatic treatment of verbal memory deficits in patients with mild cognitive impairment or even in patients of the early phase of Alzheimer's disease?*

To examine this question, it may be promising to explore the effects of low doses of fludrocortisone in patients with mild cognitive impairments (MCI) as investigational intervention to improve verbal memory. Furthermore, also the antihypertensive effects of fludrocortisone should be taken into consideration, since it is well-known that low blood pressure is a major risk factor for dementia among patients with MCI (C. Qiu, von Strauss, Fastbom, Winblad, & Fratiglioni, 2003). Thus, it seems warranted to suggest fludrocortisone for investigation as add-on treatment in MCI, given that deficits in hippocampal-related verbal memory figure prominently in MCI (Collie & Maruff, 2000). To sum up, the MR is a fruitful novel target in disorders characterized by disturbed HPA-activity, cognitive deficits, hypotension and mood problems, which are all characteristics that can be found in patients with MCI.

Finally, according to the biopsychosocial model (Engel, 1977) and "psychosocial genomics" (Kandel, 1998) there are also further genetic variables like different NR3C2 variants, environmental or biographic variables that may all play a role in stress-related disorder (Pagliaccio et al., 2014) and that have not been discussed extensively in this dissertation. To further examine and explore the potential influence of such variables is also an important and promising desideratum.

6.4 Conclusion

The aim of this dissertation was to detect important further facets of the MR in the human brain and to help disentangle the complex interaction of GR and MR. The conducted studies give novel information about the link between neurophysiological underpinnings of MR functioning and psychological phenomena like cognition, mood and social cognition. To put it in a nutshell, the dissertation examined three main research questions (section 2.1).

The first research question was: *Is the state-of-the-art hormone replacement therapy with synthetic MR and GR agonists on a par with normal endogenous cortisol with regard to neuropsychological function in patients with Addison's disease?* Besides verbal learning, there were no clinical significant impairments due to replacement

therapy, so that the current state-of-the-art hormone substitution practice was reassured. Yet, there were still subjectively reported mild concentration deficits and a decreased quality of life (Schultebraucks et al., 2015)

The second research question asked: *What are the acute effects of high MR occupation compared to low MR occupation with regard to neuropsychological functions, in particular, with regard to prefrontal cortex- and limbic structure-related functions like cognition and mood in patients with Addison's disease?* We found that high MR occupation has beneficial effects on cognitive performance in hippocampus- and prefrontal cortex-related cognitive domains as well as on self-reported mood. These results were found, even after skipping the daily dose of fludrocortisone only once.

The third research question was: *What is the role of the MR on more specialized domains like social cognition in young healthy subjects?* We found that MR stimulation leads to a shift in selective attention towards sad faces in our sample of young healthy subjects. However MR stimulation has no influence on emotion recognition.

In sum, it has been shown that the MR plays an essential role on cognitive functioning and mood in patients with Addison's disease as well as on social cognition in healthy subjects. Therefore, we confirm and extend previous findings that the MR is important for hippocampus-dependent and prefrontal cortex-dependent cognitive functioning and mood as well as for modulating quick, automatic emotional processing. These results fit very well to previous animal and human studies with healthy participants and patients with psychiatric disorders.

A novel insight is that an adequate long-term hormone substitution with fludrocortisone and hydrocortisone had no clinically significant detrimental effects on cognitive performance in patients with Addison's disease. Moreover, it is also new that patients with Addison's disease showed worse cognitive performance in hippocampus-related cognitive domains, the higher their blood pressure is and that this relationship is dose-dependent.

As has become clear, examining MR functioning is indeed a very complex but also very important topic, since it has many clinical implications. It is well known that MR function in patients with psychiatric disorders after chronic stress exposure can be compromised and that the selection of respective coping styles can become inappropriate (de Kloet, 2014; de Kloet et al., 2016). Therefore it is important to

reduce deficits in limbic MR function by potential treatments like for example fludrocortisone administration.

Our results confirm that the MR/GR balance is of extraordinary importance, since an imbalance can lead to cognitive and emotional alterations, which is important for the quality of life. In conclusion, the results indicate that MR stimulation has beneficial effects on cognitive function in healthy participants as well as depressive patients (Otte et al., 2015) or, as shown in my dissertation project, in patients with Addison's disease (Schultebraucks, Wingenfeld, et al., 2016). Due to the influence of MR on cognitive functioning and mood, an optimal hormone substitution in patients with Addison's disease is indispensable (Schultebraucks et al., 2015; Schultebraucks, Wingenfeld, et al., 2016).

Furthermore, we could show that the MR plays an important role in quick and automatic emotional processing like selective attention (Schultebraucks, Deuter, et al., 2016). This knowledge is of high importance, because selective attention is not only crucial for social cognition in healthy participants, but is also closely linked to psychiatric disorders like social phobia and depression (Heeren, Mogoaşe, Philippot, & McNally, 2015; Joormann & Gotlib, 2007; Kircanski, Joormann, & Gotlib, 2015; Mogg, Philippot, & Bradley, 2004). For future research pending questions with regard to the MR effects on such neuropsychiatric condition are still unanswered. It seems very promising to further examine the differential role of genomic MR effects via gene expression as well as the rapid non-genomic effects via the modulation of glutamatergic neurotransmission and synaptic plasticity in the diverse neuroanatomical structures of high MR expression. Hence, the MR has still many intricate secretes to reveal.

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Appendix

List of Figures

List of Tables

List of Abbreviations

ACTH – Adreno-corticotropic hormone

A.D. – Anno Domini

ADNA – Adrenal gland

AI – Primary adrenal insufficiency

AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

AMT – Autobiographical Memory test

ANCOVA – Analysis of covariance

ANOVA – Analysis of variance

ANS – Autonomic nervous system

APP – Amyloid precursor protein

AVLT – Auditory Verbal Learning test

B.C. – Before Christ

BDI-II – Beck Depression Inventory

BF_{01} – Bayes factor

BMI – Body mass index

bpm – Beats per minute

°C – Degree Celsius

CA – Cornu ammonis (divided into Cornu ammonis area CA1, CA2, CA3, and CA4)

CBF – Campus Benjamin Franklin

CBG – Corticosteroid-binding globulin

CCM – Campus Charité Mitte

CRH – Corticotropin-releasing hormone

d.h. – dass heißt (i.e. in English)

DHEA – Dehydroepiandrosterone

DGPs – German Psychology Association

EDP – Emotional dot-probe task

e.g. – Exempli gratia

etc. – Et cetera

°F – Degree Fahrenheit

FER – Facial emotion recognition task

GABA – Gamma-aminobutyric acid

GR – Glucocorticoid receptor

HIPPO - Hippocampus

HPA-axis – Hypothalamic-pituitary-adrenal-axis

HTR-FRET – Homogenous time-resolved fluorescence resonance energy transfer

i.e. – Id est

HYP - Hypothalamus

JASP – Officially JASP is no acronym, but a name. Unofficially, it stands for Just Another Statistics Program

KO mice – Knock-out mice (genetically modified mice)

MC – Matched controls

MCI – Mild cognitive impairments

MDBF – Multidimensional Mood State Questionnaire, i.e. Mehrdimensionaler Befindlichkeitsfragebogen

MDBF GS-Scale – Mood ("Gute Stimmung, schlechte Stimmung")

MDBF WM-Scale – Vigilance/ fatigue ("Wachheit, Müdigkeit")

MDBF RU-Scale – Composure/ restlessness ("Ruhe, Unruhe")

mg – Milligram

mg/kg – Milligram per kilogram

mGR – Membrane-bound glucocorticoid receptor

mmHg – Millimeter of mercury

ms – Millisecond

mMR – Membrane-bound mineralocorticoid receptor

MR – Mineralocorticoid receptor

MRI – Magnetic Resonance Imaging

mRNA – Messenger ribonucleic acid

mPFC – Medial prefrontal cortex

NCT – Number-Combination Test

nGR – Nuclear glucocorticoid receptor

NMDA receptor – N-methyl-D-aspartate receptor

nmol/L – Nanomol per liter

nMR – Nuclear mineralocorticoid receptor

NR3C1 – Nuclear Receptor Subfamily 3 Group C Member 1

NR3C2 – Nuclear Receptor Subfamily 3 Group C Member 2

NTS – Nucleus tractus solitarius

PHQ-9 – Patient Health Questionnaire

p.m. – Post meridiem

PTSD – Posttraumatic stress disorder

PVN – Paraventricular nucleus

rmANOVA – Repeated measures analysis of variance

ROCF – Rey-Osterrieth Complex Figure test

rs5522 – Mineralocorticoid receptor Iso/Val (rs5522) genotype

SD – Standard deviation

SKID – Structured Clinical Interview for DSM-IV

SPSS – Statistical Product and Service Solutions

vs. - versus

ZVT – Number-Combination test ("Zahlen-Verbindungs-Test")

11β-HSD2 – 11β-hydroxysteroid dehydrogenase type 2

Curriculum vitae

For reasons of data protection, the curriculm vitae is not available in the online version of this dissertation.

List of publications

Schultebraucks, K., Wingenfeld, K., Heimes, J., Quinkler, M., & Otte, C. (2015). Cognitive function in patients with primary adrenal insufficiency (Addison's disease). *Psychoneuroendocrinology*, *55*, 1-7.

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Schultebraucks, K. & Roepke, S. (in preparation). The influence of heart rate variability on intrusive memory using the trauma film paradigm.

Schultebraucks, K. & Roepke, S. (in preparation). Does psychosocial stress before trauma influence the development of intrusive memories?

Duesenberg*, M., Schultebraucks*, K. & Roepke, S. (in preparation). Imagery about suicide in patients with borderline personality disorder with and without PTSD and patients with depression. (*shared first authorship)

Piber, D., Schultebraucks, K., Mueller, S. C., Deuter, C. E., Wingenfeld, K. & Otte, C. (2016). Mineralocorticoid receptor stimulation effects on spatial memory in healthy young adults: a study using the virtual Morris Water Maze task. *Neurobiology of Learning and Memory*, 136, 139-146.

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Wingenfeld, K., Kuehl, L.K., Boeker, A., Schultebraucks, K., Ritter, K., Hellmann-Regen, J., Otte, C. & Spitzer, C. (under review). Stress reactivity and its effects on subsequent food intake in depressed and healthy women with and without adverse childhood experiences.

Congress contribution:

PuG 2016	Schultebraucks, K., Deuter, C. E., Duesenberg, M., Schulze, L., Hellmann-Regen, J., Domke, A., Lockenvitz, L., Kuehl, L. K., Otte, C. & Wingenfeld, K. (2016). Selective attention to emotional cues and emotion recognition in healthy subjects: the role of mineralocorticoid receptor stimulation. Poster at the 42th Annual conference „Psychologie und Gehirn“
DGPPN 2015	Schultebraucks, K., Wingenfeld, K., Quinkler, M. & Otte, C. (2015). Cognitive function in patients with primary adrenal insufficiency (Addison’s disease) and the role of mineralocorticoid receptors. Poster at the DGPPN congress (German Association of Psychiatry, Psychotherapy and Psychosomatics)
ISPNE 2015	Schultebraucks, K., Wingenfeld, K., Quinkler, M. & Otte, C. (2015). Cognitive function in patients with primary adrenal insufficiency (Addison’s disease) and the role of mineralocorticoid receptors. Poster at the 45th Annual ISPNE Conference in Edinburgh
DGE 2015	Schultebraucks, K., Wingenfeld, K., Quinkler, M. & Otte, C. (2015). Cognitive function in patients with primary adrenal insufficiency (Addison’s disease). Poster at the 58th Annual Meeting of the German Society for Endocrinology in Lübeck.

Endocrinological colloquium	Schultebraucks, K., Wingenfeld, K., Quinkler, M. & Otte, C. (2014). Cognitive function in patients with primary adrenal insufficiency (Addison's disease). Oral presentation at the interdisciplinary endocrinological colloquium in Berlin:
DGPPN 2014	Schultebraucks, K., Wingenfeld, K., Quinkler, M. & Otte, C. (2014). Cognitive function in patients with primary adrenal insufficiency. Poster at the DGPPN Congress (German Association of Psychiatry, Psychotherapy and Psychosomatics).
BNF 2014	Schultebraucks, K., Wingenfeld, K., Quinkler, M. & Otte, C. (2014). Cognitive function in patients with Addison's disease. Poster at the Berlin Neuroscience Forum.
EFCAP 2012	Schultebraucks, K. & Dahle, K.-P. (2012). Improving the prediction of criminal recidivism by exploring information of crime scenes in juvenile homicidal offenders. Oral Presentation at the 3rd Congress of European Association for Forensic Child & Adolescent Psychiatry, Psychology & other involved professions (EFCAP).

Eidesstattliche Versicherung (statement of authorship)

Ich versichere, dass ich die vorgelegte Arbeit selbstständig und ohne unerlaubte Hilfe angefertigt habe. Ich habe die vorliegende Dissertation an keiner anderen Universität eingereicht und besitze keinen Doktorgrad im Fach Psychologie.
Die Promotionsordnung der Freien Universität Berlin vom 27.10.1998, zuletzt geändert am 02.12.2008 veröffentlicht im Amtlichen Mitteilungsblatt Nr. 60/2008 ist mir bekannt.

Berlin, den 10. Oktober 2016

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Katharina Schultebraucks