Stress, emotion and cognition : role of mineralo- and glucocorticoid receptors

Brinks, V.

Chapter 1

General introduction

Outline

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1.2 Brain areas vulnerable for corticosteroid action
1.3 Corticosteroid action on emotion and cognition
1.4 Interaction between emotion and cognition
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Stress is a potent modulator of emotional and cognitive functioning. When exposed to stress during a short period, it influences emotion, learning and memory of the stressful event in such a manner that is beneficial for adaptation and avoidance of similar stressful situations in future.
Stress is generally described as any disturbance to the body, either real or imagined, that interferes with homeostasis. These disturbances or stressors elicit a cascade of neuroendocrine events including the fast activation of the sympatho-adrenomedullary stress system and the slower activation of the hypothalamus-pituitary-adrenal (HPA) axis. Corticosteroids are secreted from the adrenals as a result of HPA-axis activation and subsequently facilitate recovery from stress via negative feedback. Corticosteroids (cortisol in man, corticosterone in rats and mice) bind to two types of nuclear receptors which then modulate gene transcription; the high affinity mineralo- (MR) and tenfold lower affinity glucocorticoid receptor (GR). Both MR and GR are located in brain areas involved in emotion, learning and memory, and correspondingly influence emotional and cognitive functioning.

Besides exerting positive effects on emotion and cognition, stress is mostly known for its negative effects. When being exposed to stress for a prolonged period (chronic) or when exposed to severe stress, some individuals develop stress-related diseases such as depression or post traumatic stress disorder (PTSD). These disorders are characterized by altered emotional and cognitive processing together with disrupted glucocorticoid function [6].
This raises the following questions: (1) general: Why are some individuals more prone to the development of stress-related diseases? And (2) more specific: Are the glucocorticoid stress system, emotion and cognition interdependent? And what is the role of MR and GR in emotional and cognitive processes?
The assessment of the interaction between emotion, cognition and the glucocorticoid stress system will be helpful in understanding the pathogenesis of stress-related diseases and perhaps offers new opportunities for treatment.

The main objective of this thesis is therefore to study the interaction between the glucocorticoid stress system, emotion and cognition by focussing on MR and GR functions.

In section 1.1 of this thesis, the molecular and cellular mechanisms of corticosteroid action are described, followed by an overview of the brain areas that are target for corticosteroid action (1.2), corticosteroid effects on emotion and cognition (1.3), the interaction between emotion and cognition (1.4), (behavioural) mouse models to measure corticosteroid action on emotion and

cognition (1.5), translational approach (1.6), culminating in presenting the scope and outline of this thesis (1.7).

1.1 Molecular and cellular mechanisms of corticosteroid action

Knowledge of the stress system, including the neurobiological and anatomical background, is fundamental for understanding its role in emotion and cognition. The designs used for behavioural experiments are based on this knowledge. Next sections discuss the stress system including molecular and cellular mechanisms.

1.1.1 The main players of the hypothalamus-pituitary-adrenal (HPA) axis

During basal conditions, the neurons of the paraventricular nucleus (PVN) of the hypothalamus stimulate the secretion of corticotropin releasing hormone (CRH), vasopressin (VP) and other neuropeptides. CRH and VP together activate the release of adrenocorticotropin (ACTH) from corticotrope cells in the pituitary glands. ACTH is transported by the blood to the adrenal cortex, which in turn secretes corticosteroids including cortisol (in man, corticosterone in rodents). Due to their lipophilicity, corticosteroids enter the brain and bind to two distinct types of receptors; the mineralocorticoid (MR) and glucocorticoid (GR) receptor.
Corticosterone is secreted in hourly pulses that increase in amplitude towards the circadian activity period. Superimposed on this ultradian rhythm is the response to a stressor, in which the neurons of the PVN enhance CRH and VP secretion, leading to increased ACTH and corticosteroid levels in the blood. A subsequent negative feedback circuitry reduces corticosteroid secretion from "stress-induced" to basal levels (figure 1) [12].

1.1.2 The corticosteroid receptors

Corticosteroids bind to two types of central steroid receptors; the high affinity mineralocorticoid receptor (MR) and tenfold lower affinity glucocorticoid receptor (GR) [13-15]. As a consequence, the MR is extensively occupied due to hourly corticosterone pulses, while substantial GR occupation occurs at ultradian peak levels and following a stressor. MR and GR mediate corticosteroid action as transcription factors and influence HPA axis activity with distinct functions. MR suppresses basal corticosterone pulsatility and the HPA response to a stressor. The latter is due to interference with fast feedback of HPA activity [16]. GR in contrast facilitates the termination of a stress response via a negative feedback loop [17;18].
The MR (116 kD) and GR (97 kD) genes are ancestrally related [19] and show similarities in gene structure; the ligand binding domain has a 57 % amino acid identity and the DNA binding domain is 94% similar between the MR and GR gene [20]. Both genes can be translated to multiple mRNA isoforms due to

alternative splicing and various polymorphisms [21;22]. In addition, post translational modifications such as phosphorylation can result in multiple MR and GR proteins, which might differentially affect metabolism, neuroendocrinology, behaviour and contribute to stress-related diseases [22-26].

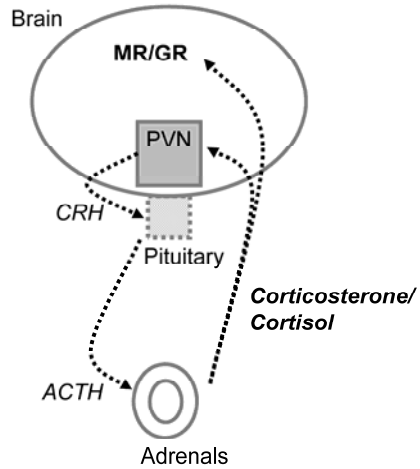

Figure 1. A schematic overview of the hypothalamus-pituitary-adrenal axis. Arrows indicate feedforeward and feedback regulation of hormone secretion.

1.1.3 Genomic effects of corticosteroids

After binding corticosterone, MR and GR dimerize to form mono- and dimers [27-29] These dimers, which mediate corticosteroid action as transcription factors, bind to glucocorticoid response elements (GRE) and result in transactivation or transrepression of gene expression [30]. Transactivation follows GRE binding in the vicinity of gene promoters. In this case, gene expression can be either enhanced or lowered by increasing or decreasing the frequency of transcription. Transrepression takes place when monomers bind to transcription factors (TF) and inhibit transcriptional activity of the target gene (figure 2).

A large part of the corticosterone responsive genes in the hippocampus is regulated by either activated MR or GR [31]. However, MR and GR heterodimers are thought to express an additional functionality in transcriptional regulation of corticosteroid responsive genes [27;29]. This shows the complexity and diversity of MR and GR dependent mechanisms to evoke changes in gene transcription.

The changes in gene transcription due to MR and GR activation follow a distinct time course [32]. Morsink and colleagues have shown that one hour after GR activation (in addition to MR) all affected genes are down regulated, presumably

via transrepression, while at three hours the affected genes are both up and down regulated. At 5 hrs, gene expression is almost back to baseline [32]. These corticosteroid regulated genes include immediate early genes [33] and MR [34], and are related to signal transduction, G-protein coupled receptor protein signalling pathway and protein biosynthesis [32].

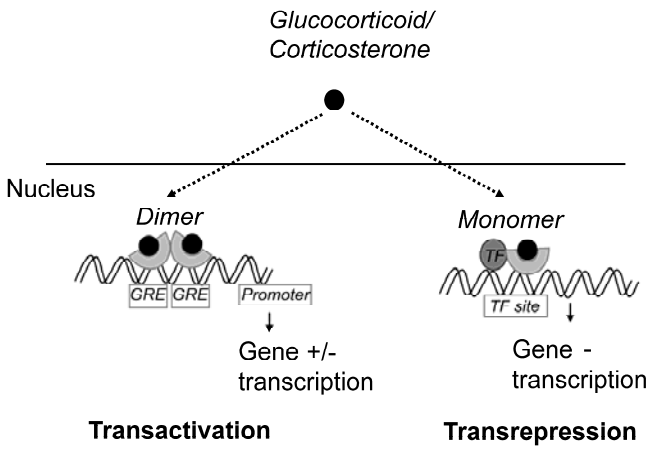

Figure 2. Schematic view of transactivation and transrepression of target genes due to corticosterone binding to its receptors, the mineralo- (MR) and glucocorticoid receptor (GR). MR and GR homo- and dimers bind to glucocorticoid responsive elements (GREs) on the DNA and inhibit or increase gene transcription.

1.1.4 Long term potentiation

Corticosteroids also influence the cellular mechanism which models learning and memory processes *ex-vivo*; long term potentiation (LTP) [35]. LTP is defined as a long lasting strengthening of neuronal connections following (high frequency) stimulation. It is divided into early, protein synthesis independent LTP directly following stimulation (min-hours), and late protein synthesis dependent LTP, which can last from hours up to months [36-38].

LTP is most investigated in the hippocampus. Here, as in other brain areas glutamate is the major excitatory neurotransmitter and its receptors, N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) are critical in inducing LTP.

Corticosterone can exert fast effects on LTP. It quickly increases the release probability of glutamate containing vesicles in a non-genomic manner [39] and increases the chance that alterations in glutamate release results into enhanced firing rates [40]. Karst and colleagues have shown that such non-genomic effects involve membrane located MR [39].

However, the majority of studies present focus on the slow gene-mediated effects of a stressor and corticosteroids. Overall, these experiments show that corticosteroid effects on LTP in the cornu ammonis 1 (CA1) area of the hippocampus (section 1.2.1) follow an inverted U-shape. Low levels of corticosterone sufficient to activate part of the mineralocorticoid receptors are associated with efficient LTP [41-44], whereas periods of stress impair LTP induction [for review: 45]. This clearly shows the suppressing effect of GR activation on LTP induction. Interestingly, corticosteroid effects on synaptic transmission in another part of the hippocampus, the dentate gyrus (DG), do not follow an inverted U-shape [46].
Recently, Olof Wiegert demonstrated that timing of corticosterone is also crucial for its effects on LTP. Corticosterone has fast facilitating effects on LTP when given simultaneous with a high frequency stimulation, however this effect is absent when given before or after repetitive stimulation [47].

In summary, corticosteroids act via distinct receptors, MR and GR, inducing slow genomic actions via transcriptional regulation but also exerting fast non-genomic effects on LTP. These molecular and cellular mechanisms provide the basis for the corticosteroid effects on emotion and cognition.

1.2 Brain areas sensitive for corticosteroid action

The hippocampus, amygdala and prefrontal cortex (PFC) are brain areas involved in emotion and cognitive functions (figure 3). These areas are very connected and sensitive to corticosteroid action due to abundant MR and GR expression. Since the experiments described in this thesis address the function of these brain areas, this section will focus on their role in emotion and cognition.

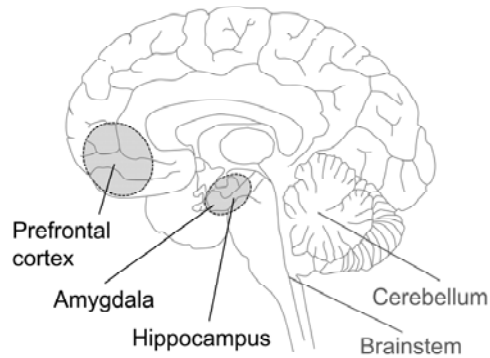

Figure 3. Location of the hippocampus, amygdala and prefrontal cortex in the human brain.

1.2.1 The hippocampus

The main function of the hippocampus is the processing of contextual information [48] which includes spatial learning and memory, but is also involved in fear-related behaviour through connections with the amygdala [49;50].

The hippocampus is part of the limbic system and is situated in the temporal lobe. It consists of a heterogeneous population of neurons and glia cells which form distinct subfields: the dentate gyrus (DG) and cornu ammonis areas (CA1, CA2 and CA3). The DG, CA3 and CA1 areas are connected by a trisynaptic circuit [51;51]. The DG is connected to the entorhinal cortex via the perforant path, and sends information to the CA3 via mossy fibers. The CA3 in its turn is connected to the CA1 via the Schaffer collaterals. This trisynaptic circuit is often used to measure LTP (section 1.1.4).

Most areas contain cells which are characterised by place specific firing patterns and are believed to play a role in navigation and formation of a spatial map, however the naming "space cells" is restricted for the principal cells of the CA1 and CA3 area [52]. The hippocampal subfields express distinct functionality in information processing. While the DG and CA3 areas are involved in encoding of spatial information [53;54], the CA1 is involved in temporal information processing [55]. MR is highly expressed in all hippocampal areas, GR is predominantly expressed in the DG, CA1 and CA2 [56;57].

Box 1. Hippocampal volume of people suffering from stress-related diseases.

Hippocampal volume of patients with depression or PTSD

Several studies have shown that patients suffering from stress related diseases such as major depression or post traumatic stress disorder have a smaller hippocampal volume compared to healthy subjects [4;5], often correlated with impaired memory performance [10]. Interestingly, when PTSD patients undergo treatment with the antidepressant paroxetine (a selective serotonin reuptake inhibitor), hippocampal volume and memory performance recover in parallel [10]. Although small hippocampal volume may be a pre-existing risk factor for stress related diseases, (traumatic) stress could also reduce hippocampal volume.

1.2.2 The amygdala

The amygdala affects the processing of positive and negative stimuli including the autonomic response to emotional stimuli [58-63]. It is predominantly studied for its role in (auditory) fear conditioning, which uses aversive stimuli to measure emotional learning and memory [64-67].

The amygdala, as the hippocampus, is located in the temporal lobe and consists of several nuclei with specific functions. In these sub-nuclei, corticosteroid

receptor expression differs: GR is most expressed in the central and lateral areas, while the MR, which is less abundantly present, is mainly expressed in the corticomedial areas [68;69].

Several hormones beside corticosteroids influence amygdala functioning. One of them is CRH. This hormone facilitates attention to external events, sustains fear-related memory and when increased for an extended period, possibly even contributes to anxious depression [70-72].
The amygdala is also strongly under influence of catecholamines. These hormones are released from the adrenal medulla as a part of the fast sympatho-adrenomedullary stress response and indirectly affect amygdala processing [73-75]. Even more, catecholaminergic activation of the basolateral amygdala is necessary for correct corticosteroid functioning in hippocampal memory [75-77]. This implies that an event has to activate the amygdala, having an emotional "load", for optimal learning and memory of that event. Correspondingly, many studies have shown that emotional stimuli are better learned and remembered than neutral ones [78-80].

Box 2. Examples of amygdala functioning in humans.

Emotion and amygdala function: activation, stimulation and disruption

Presentation of faces with fearful or happy expressions changes the activity of the amygdala. This response is increasing with fearfulness, while it decreases with increasing happiness [3]. Electrical stimulation of the amygdala evokes both negative and positive emotions, accompanied by physiological responses, e.g. skin conductance [7]. Patients with amygdala damage are unable to correctly address emotional value to fearful and happy faces. Even more surprising, these patients give positively biased evaluations for negative facial expressions [11].

1.2.3 The prefrontal cortex

The prefrontal cortex (PFC) also influences emotional and cognitive functioning. The functions of the prefrontal cortex involve decision making, inhibition, behavioural flexibility, capacity to deal with novelty and goal directed behaviour. Overall, these functions allow to selectively respond to relevant external stimuli [81;82].
The PFC is located in the anterior part of the brain just above the orbit of the eyes. Strictly it is not part of the limbic system, but has strong connectivity with limbic structures. The PFC consists of several areas (medial, orbital and lateral) with distinct functions. The infra- and prelimbic areas of the FPC have been associated with diverse emotional and cognitive processes such as flexibility

during novel situations [83] and through connections with the amygdala they can also affect anxiety-related behaviour [84-86].
GR is expressed in all PFC areas, while MR expression is restricted to the infralimbic and prelimbic areas [69].

Box 3. An early case report of frontal lobe damage.

Phineas Cage

The case of Phineas Cage is one of the earliest descriptions of personality and behavioural changes following frontal lobe damage [2]. He was a railway worker in the USA around 1850 that became famous after surviving an explosion resulting in an iron bar planted in the front part of his head. After recovery, Phineas displayed impaired (irrational) decision making and a change in emotional processing. He was unable to keep his job as foreman of railway workers.

1.2.4 Connectivity between the hippocampus amygdala and PFC

The hippocampus, amygdala and PFC are extensively connected. To elaborate on this connectivity without presenting the enormous wealth on studies, the next section shows a schematic overview of some important connections (figure 4) and discusses several interacting connections between these brain areas.

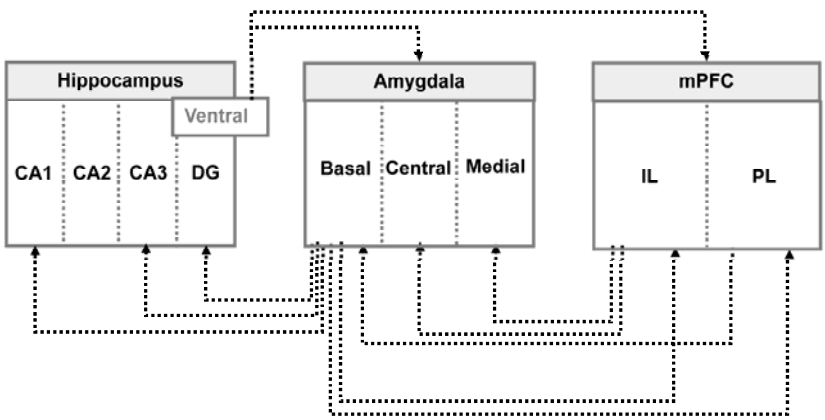

Figure 4. Schematic presentation of some important neural connections between the hippocampus, amygdala and PFC. References: [85;87-91].

Yaniv and colleagues have shown that neural activity in the entorhinal cortex, simultaneously influences LTP in both the hippocampus and amygdala [92], indicating interacting connectivity between these two areas. This is supported by high frequency stimulation in the basolateral part of the amygdala, which evokes LPT in the hippocampus [93;94]. Ishikawa and colleagues even more

showed that connection between the hippocampus and amygdala converge and interact in neural activity of the PFC. This leads to the believe that simultaneous activation of hippocampus and amygdala neurons may be important for enhancing medial PFC activity [90].

In summary, the hippocampus, amygdala and PFC have distinct functionality including contextual (time and place) and emotional processing and selective responses to relevant stimuli. They are sensitive to corticosteroids, are heavily connected and interact in several behavioural processes. This provides a base for interdependent actions of the stress system, emotion and cognition.

1.3 Corticosteroid action on emotion and cognition

Stress and corticosteroids activate MR and GR in the brain and influence different aspects of emotion and cognition. The next section discusses stressor and corticosteroid induced behavioural effects measured in rodents, first focussing on emotional and cognitive processes that are addressed in this thesis and second concluding with the specific role of MR and GR.

1.3.1 General note on behavioural observation in rodents

Before discussing which behaviours are under influence of corticosteroids, it should be realised that cognitive and emotional processes of mice are deduced from activity patterns. While techniques in molecular research have advanced, behavioural analysis is still often performed with limited behavioural data on these activity patterns. In this thesis we will extend behavioural analysis by performing in depth behavioural observation. In this case, conclusions are drawn from a broader behavioural spectrum.

1.3.2 Behavioural reactivity: Unconditioned response

Stressors and corticosteroids modulate exploration and locomotor activity. Exploration, which can be divided into general and directed exploration, is measured by total movement in the setup, walking patterns and rearing behaviour (figure 5); general exploration [95;96], or by the specific exploration of an object; directed exploration [97;98]. Locomotor activity is the total amount of horizontal movement in the setup.

Corticosteroids can have enhancing and suppressing effects on general exploration and locomotor activity [99]. Acute corticosteroid treatment increases locomotor activity [100-104]. This possibly reflects an active coping strategy [104], or anti-depressive actions when using an animal model for behavioural despair such as forced swim [105;106]. In contrast, extremely high corticosterone concentrations or chronic stressors are associated with suppressed locomotion and increased immobility [105-107]. Interestingly, when

using acute stressors instead of pharmacological corticosteroid manipulation, also suppressing effects on locomotor activity are observed. These effects are dependent on the type of stressor [108-110]. Whether reduced locomotor activity is an expression of high emotionality, as suggested in several studies, will be addressed in **chapter 3**.

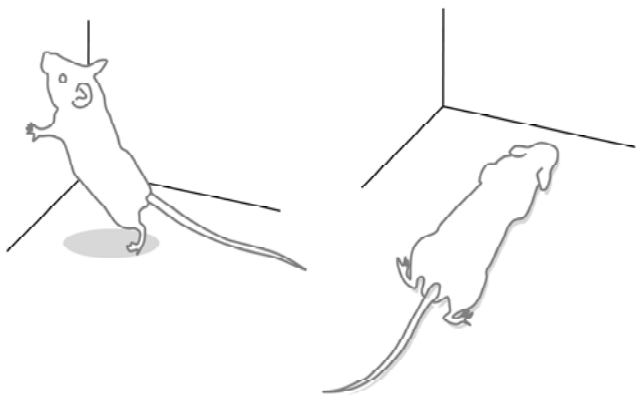

Figure 5. Rearing behaviour (left). The mouse stands on its hind legs, usually with the front legs against a wall, although rearing in an open area is also possible. Stretched attend posture (right). The mouse stretches it body horizontally while keeping its hind legs at the same position.

Unfortunately, data on how corticosteroids or stressors affect directed exploration as part of unconditioned response are very sparse. This is mainly due to the lack of environmental enrichment in the behavioural setups used to measure exploration and locomotor activity. However, directed exploration is often measured in the context of a learning task, e.g. conditioned response, by object recognition or platform finding in the watermaze.

The expression of negative emotions of anxiety and fear form another part of unconditioned behaviour. Anxiety-related behaviour is measured by avoidance of unprotected zones in a setting such as the open field, elevated plus maze (section 1.5.1) and light/dark box [111-115], meaning that locomotor activity and exploration can be confounding factors in measuring anxiety-related behaviour.

Fear-related behaviour is most commonly measured in learning tasks, expressed as freezing, scanning and startle response both after and in expectation of an aversive stimulus. Freezing is defined as total immobility of the animal and scanning is defined as total immobility except for head movement. Both are measures of immobility, however freezing is more severe due to the complete lack of environmental interaction.

At the psychological level, anxiety-related behaviour belongs to trait and state anxiety. Trait anxiety is a basal expression of innate anxiety and depends on

epigenetic influences [116;117], while state anxiety is measured after an exposure to or expectation of a mild aversive stimulus. Unfortunately, most anxiety-related tests in rodents involve placing the animal in a novel environment, which by itself acts as an anxiety enhancing stimulus and thus makes testing for trait anxiety very difficult. For this reason, the next section will only refer to state anxiety. Stressors and corticosteroid treatment enhance anxiety-related behaviour in different behavioural tasks [118-122]. Correspondingly, prolonged exposure to stressors increases fear-related behaviour [123;124]. Interestingly, a study by Skorzewska shows that an acute stressor lowers fear-related behaviour, although exploratory behaviour is increased [124]. This might be interpreted as active fear coping. Besides unconditioned responses to a one-time aversive stimulus, fear-related behaviour is also measured in the context of a learning task such as fear conditioning (section 1.5.1).
Corticosteroids and stressors can also influence risk assessment. This is defined in the mouse as stretched attend posture (figure 5). In general, risk assessment is enhanced by acute stressors and corticosteroid treatment [103;118;125].

1.3.3 Learning and memory: Conditioned response

When addressing the range of corticosteroids and stress effects on cognitive processes of learning and memory such as acquisition, consolidation, retrieval and extinction (short definition in box 4), three major influencing factors can be distinguished.

Box 4. Cognitive processes discussed in this thesis.

Cognitive processes (in short)

Cognitive processes of learning and memory discussed in this thesis (acquisition, consolidation, retrieval and extinction) take place in different time periods during and after an event:

1. During: Acquisition, gain of information about the event (learning)
2. Directly after - hours: Consolidation, memory formation about the event
3. Short/long term: Retrieval, recalling information that is stored
4. Short/long term: Extinction, decrease of memory-related behaviour due to repeated exposure (new learning)

Processes 1, 3, and 4, but not 2, can be deduced from the behaviour of the animal.

The first major factor is the **timing/duration** of the stress hormone action. Stress and corticosteroids facilitate memory formation, but only when the stressor or corticosteroid modulation is closely linked to the learning context [126]. For example, when given directly before a learning task, corticosterone

facilitates consolidation [127]. However, corticosteroid treatment in the period prior to memory testing impairs subsequent performance [128;129]. This impairment is often discussed as a corticosterone effect on memory retrieval [129;130], but another attractive possibility is that under the influence of the hormone an attention shift occurs towards the novel, distracting stimulus, thereby facilitating the processing of this "other" information.
The duration of corticosterone treatment or stressor is another important modulator of conditioned response. While an acute stressor can enhance acquisition, chronic stressors or corticosterone treatment impair memory formation and retrieval [131-133].
The second major factor is the **corticosteroid receptor mechanism**. Differential expression patterns and binding properties of MR and GR in the brain have consequences for cognitive processing. When using a spatial orientation task which depends on hippocampal functioning, corticosterone- and stressor mediated effects follow an inverted U-shape dependency [134-137]. Extremely low or high corticosteroid concentration, indicating relative high MR or GR function, impairs memory, while intermediate corticosteroid doses result in optimal memory performance. If the task used includes a large emotional component and thus heavily relies on amygdala functioning, stressors and corticosteroids affect memory following a linear relationship[138].
The third factor is **gender**. Cognitive (and emotional) functions of female and male rodents are differentially affected by corticosteroids and stressors [139;140]. Sex hormones like estrogens, strongly affect cognitive functioning [141;142] and these effects most likely interact with corticosteroids.

1.3.5. Specific MR and GR function in emotion and cognition

MR and GR are potent modulators of emotion and cognition with partly overlapping but also distinct functionality. MR, having high affinity for corticosteroids, is continuously occupied but can apparently also exert fast non-genomic influences on behaviour during high corticosterone concentrations. MR controls the initial behavioural response (behavioural reactivity) which is then, due to slow activation of the low affinity GR, processed during the consolidation period to facilitate memory for that event.
MR and GR also function in balance. This means that dysfunction of either receptor results in enhanced functioning of the other, hampering the interpretation of such effects. Is the effect due to relative increase of one receptor or due to relative decrease of the other?

MR modulates the behavioural response towards novelty. Novelty is represented by exposure to an unfamiliar environment, but can also be defined

as introducing or removing an object in a familiar setting. Behaviour in both novelty conditions is influenced by MR.
When introducing an unknown object into a familiar environment, MR knockout or overexpression alters exploration of this object [143;144]. Likewise, when removing a familiar object in the watermaze, MR antagonism and overexpression changes swimming patterns and escape strategy [143;145;146].
When placed in a novel experimental setting, MR antagonism lowers corticosterone induced locomotion, changes object recognition [100] and lowers anxiety-related behaviour [147-149]. In contrast, MR overexpression can also lower anxiety-related behaviour [144;150;151]. These findings illustrate the U-shaped dose-dependency of MR-mediated effects, in which complementary GR-mediated actions also seem to participate.
It would be expected that MR modulation and therefore changing behavioural reactivity towards novelty would affect subsequent learning and memory. A change in behavioural reactivity towards novelty likely reflects different perception and focus of attention. This difference in perception and attention could alter the information that is gained about the novelty, leading to consolidation of different information and thus different memory. Indeed, several studies show that MR overexpression and pharmacological activation is associated with enhanced memory consolidation [144;151;152], while less MR activity diminishes spatial learning [146] and memory [143;153].

GR influences cognitive processes by facilitation of consolidation. This is shown by diminished spatial memory in mice with chronic inactivation of whole brain GR (knockout), GR dim/dim mice, mice with less GR expression and acute intracerebroventricular injections of a GR antagonist [127;145;154;155]. GR function has also been extensively studied in fear associated learning and memory. Here, pharmacological blockade of GR in non stressed and chronic stressed animals attenuates the expression of contextual fear response [123;156]. The GR mediated effects on fear (memory) are area specific; acute pharmacological blockade of the GR in the dorsal hippocampus of rats facilitates spatial learning [157], while GR blockade in the ventral hippocampus decreases long term contextual/spatial fear memory [158]. GR in the amygdala is necessary for auditory fear consolidation [67]. This corresponds to the role of the hippocampus in context dependent fear conditioning and the role of the amygdala in cue-related fear conditioning (section 1.5.2).
GR can also influence anxiety-related behaviour. Overall, less GR function lowers anxiety-related behaviour [159-162], while increased GR activation correlates with high anxiety-related behaviour [159].

In summary, stressors and corticosteroids affect emotion, learning and memory depending on duration, dose and gender and are only effective in the context of a learning task. The effects exerted by the steroid are mediated by MR and GR. Via MR, corticosterone influences the behavioural response towards a new or changing situation, while additional activation of GR facilitates memory consolidation.

1.4 Interaction between emotion and cognition

Central to cognitive emotional interactions are the above mentioned brain areas, i.e. hippocampus, amygdala and PFC, which have a high degree of connectivity (section 1.2). Emotional and cognitive processes often interact and contribute together to behaviour. Examples of such interactions in humans and rodents are discussed in the following section.

1.4.1 Human

For a long time, emotion and cognition have been examined as separate entities. Just lately more and more studies have focussed on the specific interaction between emotion and cognition.

For example, exposure to an emotional picture impairs ongoing working memory processes more than exposure to a neutral picture. Furthermore, besides ongoing cognitive functions, also long term cognitive processes such as declarative and procedural memory are sensitive to emotional modulation [163]. In turn, cognitive processes change the response to emotional stimuli [164].

Studies on this interaction between emotion and cognition in stress-related psychopathology have just started. Results show that patients suffering from depression [165] and PTSD often have a memory bias for emotional information [166]. Furthermore, emotional arousal in PTSD patients hampers cognitive functions (see section 1.6). It is expected that behavioural studies will further specify how emotion and cognition are integrated in these diseases.

Besides behavioural research, also brain imaging studies support the interaction between emotional and cognitive functioning. For example, an fMRI study in healthy subjects shows that altered communication between limbic areas (amygdala), prefrontal cortex and cingulated cortex impairs cognitive processing of emotions [167]. Several fMRI studies on interacting emotional and cognitive processes focus on the prefrontal cortex [168]. These studies demonstrate that emotional states can selectively influence working memory-related neural activity in the lateral PFC [169;170].

1.4.2 Rodent

Interacting emotional and cognitive functions are also observed in mouse behaviour [171-174]. For example, pharmacologically increased anxiety

decreases working memory performance of mice in the watermaze [175], while the reduced anxiety observed after deletion of the corticotropin-releasing factor receptor 1 impairs spatial recognition memory [172]. In addition, low anxiety and good cognitive performance correlate in DBA mice, while exploration and cognitive functioning is correlated in C57BL/6J mice [171].

These findings underline the interaction between emotion and cognition, however, the involvement of the glucocorticoid stress system needs to be elucidated.

1.5. (Behavioural) tasks and animal models to measure emotion and cognition

A variety of tasks is available for measuring specific aspects of emotion and cognition in rats and mice. Some tasks focus on behavioural reactivity, while others relate to learning and memory processes. The test paradigms discussed in this thesis include "classic" tasks which are adapted and refined for (i) simultaneous measurements of emotional and cognitive parameters and (ii) discrimination of context and cue-related fear memory and its extinction. Next, the mouse models used in this thesis are described, i.e. mice of distinct strains, as well as mice with genetically manipulated MR. The last section will address the statistical approach used to handle the large amount of behavioural data.

1.5.1. Behavioural tasks

Experiments described in this thesis are based on three behavioural tasks, (i) the elevated plus maze (EPM), a "classic" test to measure unconditioned behaviour including emotional expression related to anxiety, (ii) the modified holeboard (MHB) to measure unconditioned behaviour but also simultaneously emotion and reward-related cognition and (iii) a refined fear conditioning task for testing of alternating context and cue fear memories and their extinction.

The EPM is used to measure unconditioned behaviours by estimation of the balance between anxiety-related behaviour and exploration (figure 6). This test uses the mouse's innate avoidance of open spaces, which is interpreted as anxiety behaviour. As there are no complex features in the test apparatus, aspects of behavioural reactivity such as directed exploration cannot be assessed.

The MHB provides a complex environment and therefore can be used to measure all aspects of behavioural reactivity, exploration and emotional expressions (figure 6). Introducing treats at certain locations modifies the task for additional assessment of reward stimulated learning and memory. Thus, we can simultaneously test emotional and cognitive functioning. The EPM and MHB depend on the voluntary exploration of protected and unprotected areas.

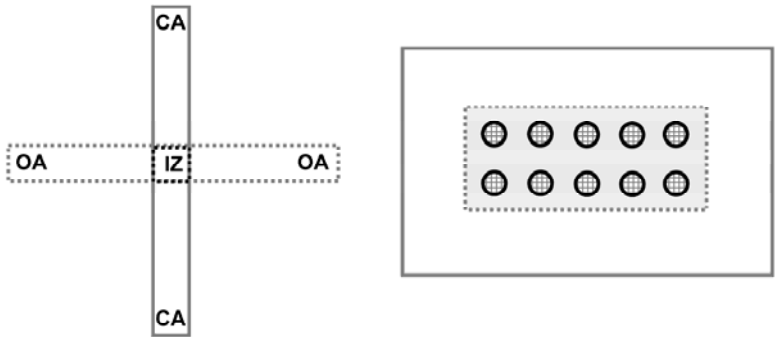

Figure 6. The elevated plus maze (EPM: left) and modified holeboard (MHB: right) seen from above. EPM: The EPM consists of an elevated platform on which four Perspex arms in the shape of a cross, and an intermediate zone are present: two arms with side walls (closed arms; CA; "safe, protected") and two arms without side walls (open arms; OA; "unsafe, unprotected") are separated by an intermediate zone (IZ). The EPM is mainly used as a one trial, short test (5 min) to measure anxiety-related, escape and explorative behaviour [176-179].
MHB: A board containing 10 cylinders is located in the centre of an open field. Thus, the board is in an unprotected unsafe zone, while the areas near the walls provide protection. Moreover, the cylinders represent objects to explore. This task can be used as a short one trial test (5 min) for anxiety-related and explorative behaviour, including both general exploration and directed exploration towards the cylinders. Baiting the cylinders with treats (bait), the MHB can be used as appetitive learning task to measure cognitive parameters such as reference and working memory [171;180]. In this case, the animals undergo a multiple trial protocol in which they have to find these baits. Visual markers of the baited cylinders can be used to assess visual-discrimination learning.

Fear conditioning is based on the classical Pavlovian conditioning paradigm and allows studying the development of fear memories and their extinction (figure 7). Fear conditioning can be used to determine the contribution of two brain systems to fear memory; the hippocampus which processes context-related fear memory and the amygdala which processes cue-related fear memory [181].

1.5.2. Mouse models

In addition to the behavioural tasks described above, this thesis describes several mouse models to study the corticosteroid action on emotion and cognition: (i) pharmacological activation or blockade of MR and GR, (ii) naturally occurring genetic variation of MR and GR in inbred mouse strains and (iii) genetic modification by MR knockout in the forebrain. Next section discusses these mouse models.

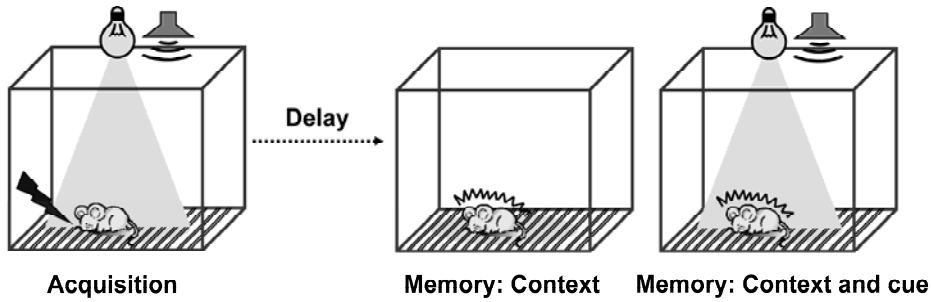

Figure 7. Schematic representation of the fear conditioning setup and protocol that are used for experiments described in this thesis. During acquisition, an unexpected aversive stimulus (electric foot-shock: unconditioned stimulus US), is given several times in association with a neutral stimulus such as a light and tone (cue; conditioned stimulus CS), in a distinct environment (context). The animal will form an association between the announcing cue and aversive stimulus but also the surrounding in which the aversive stimulus was given, i.e., formation of fear memory. After a delay the animal is placed in the same context and additionally the cue (light/ tone) is turned on in the same sequence as during conditioning, but without electric shock. This should evoke a fear response (conditioned response, CR) that is predominantly expressed as freezing (fear memory). Due to repeated exposure to context and cue without electric shock immobility behaviour is expected to decrease, i.e., extinction. Two main types of fear behaviour can be distinguished; immobility and escape behaviour. Immobility includes scanning and freezing. Scanning is defined as immobility of the body, while the head is moving horizontally from side to side. Freezing is defined as immobility of the body and head. Depending on the type of behavioural observation, either immobility (automatic; infrared/light beams) or freezing and scanning (manual) can be registered. Escape behaviour can be observed by the number of attempts to jump out of the setting.

Next to the well known use of MR and GR antagonists, a common method to differentially activate MR and GR is **replacement with corticosteroids** in animals with (almost) no endogenous corticosteroid production **(chapter 2)**. The adrenals are surgically removed and a pellet containing different corticosterone concentrations is subcutaneously implanted. In contrast to rats, mice that undergo adrenalectomy remain to produce low concentrations of corticosterone from scattered cell groups in the vicinity of the adrenals [182]. Therefore, adrenalectomized mice provide an excellent model for predominant MR activation. Different degrees of continuous GR activation can be achieved via corticosterone released from implanted pellets, while an injection results in a phasic activation of GR on the background of continuous MR activation.

Naturally occurring variances in MR and GR expression as present in selected inbred strains provide another possibility to measure MR and GR

function. For example, the Lewis and Fisher rat strains are known for their differences in stress sensitivity [183;184]. Mouse lines selected for short and long attack latency (SAL and LAL respectively) also demonstrate distinct stress system regulation [185;186].
This thesis describes a study in which BALB/c and C57BL/6J mice are characterized for stress system markers, emotion and cognition **(chapter 3)**. These strains have been originally used in immunology research to determine their resistance and immunological response to various infectious agents [187;188]. BALB/c mice have been described in the literature to be more stress reactive during mild subchronic stress compared to C57BL/6J mice [189]. BALB/c and C57BL/6J mice show different exploration patterns [180] and BALB/c mice display higher anxiety-related behaviour [189-192]. As briefly discussed later on, a proposed explanation for the difference in anxiety-related behaviour between these strains is the distinct maternal care given by the dams [193].
Data on cognitive performance of BALB/c and C57BL/6J mice is sometimes contradictive. Some studies report poor spatial learning abilities of BALB/c mice in the water maze [194-196]. However, BALB/c mice do not show inferior cognitive performance when tested in a dry maze or when multiple cognitive parameters for learning and memory are included [195;197]. Fear conditioning studies have shown that C57BL/6J mice freeze more often and display generalised freezing compared to BALB/c mice [198;199].
These strains also have distinct corticosteroid-related molecular determinants that can influence emotion and cognition. For example, BALB/c mice have lower GABA(A) receptor expression compared to C57BL/6J mice [200;201]. GABA(A) is influenced by maternal care and negatively correlates to anxiety-related behaviour [202]. BALB/c and C57BL/6J mice also differ in NMDA mediated cognitive processes in the amygdala [203]. The NMDA receptor, which is more expressed in BALB/c mice, specifically facilitates the magnitude of contextual fear acquisition [204;205]. In addition, beta-adrenoceptor expression also differs between these strains. BALB/c mice exhibit higher amygdala beta-adrenoceptor expression compared to C57BL/6J mice [206]. This receptor binds hormones which are released during the fast sympatho-adrenomedullary stress response, and therefore might suggest that BALB/c mice are more susceptible to fast stress effects on behaviour.
Overall, BALB/c and C57BL/6J mouse strains likely differ in glucocorticoid stress system (and related molecular determinants), emotion and cognition. However, also differences in the fast sympatho-adrenomedullary stress response seem to be present.

Experiments described in this thesis also include genetically altered mice with **MR ablation** in the forebrain. The advantage of these mice is the huge change

in MR function compared to naturally occurring differences in expression, so more pronounced behavioural effects are expected. Another advantage is the neuro-anatomically defined location of the genetic alteration. Although both peripheral and central targets can be selected, these MR ablated mice have forebrain-specific inactivation of the MR gene ($MR^{CaMKCre}$). This allows studying the specific function of limbic MR. The third advantage is the inducibility of gene modulation. These $MR^{CaMKCre}$ have reduced MR at postnatal day 0 and complete loss of MR at postnatal day 12 and during adulthood. They do not show any visual (appearance), acoustic and motor abnormalities compared to controls [143].
This thesis describes experiments using the $MR^{CaMKCre}$ mice to determine specific MR contribution to emotion and cognition tested in the described fear conditioning task **(chapter 6)**.

1.5.3. Statistical analysis

As a result of extended analysis of behavioural parameters of emotion and cognition, a large amount of data is generated. Besides "standard" statistical analysis, principal component analysis (PCA) will be used in order to structure the behavioural data. PCA is a statistical data reduction method that minimises multidimensional data sets and is used to explain variability among behaviours. It determines correlations between behavioural parameters which allow "clustering" of behaviours into so called factors. These correlations and factors can be used to determine which emotional and cognitive parameters interact (or are independent), and with the use of further ANOVA testing determines group or strain differences in this interaction.

1.6. Translational approach: from animal model to stress-related pathology

Nowadays, the long time separated areas of human and animal research on cognition and affect start to merge. Also the study of the implication of this research for psychopathology has just begun..
Animal models provide an opportunity to study the genetic determinants that underlie the endocrine and behavioural stress responses. They allow to determine which factors could play a role in the susceptibility or resistance to stress-related diseases, which involve emotional and cognitive disturbances.
In humans, post traumatic stress disorder (PTSD) is characterized by persistent intrusive fear memories of a stressful event, with concomitant strong emotions. Why these strong emotional memories are present; due to enhanced acquisition, stronger consolidation or impaired extinction, is unknown. In this thesis an animal model for PTSD is described using a dedicated fear conditioning design in mice with distinct MR and GR background. This design allows the study of the development, memory and extinction of strong

emotional memories in mice. Furthermore, it is possible to simultaneously assess if fear memory is generalized or specific for a predictive stimulus.
To clarify the translational approach, characteristics of PTSD with a specific focus on the changes in circulating glucocorticoids, emotion and cognition are described below.

1.6.1. Post traumatic stress disorder (PTSD)

An estimated 8 % of the world population will experience PTSD at some point in their lives. War, sexual or physical abuse, witnessing or being in a life threatening situation, like surgery, accidents or terrorist attacks, but also natural disasters like the tsunami are traumatic experiences that can result in PTSD. Prevalence of PTSD was as high as e.g., 24.4% in relief workers after the tsunami in Asia [207] and 20.9% in Israeli Yom Kippur War veterans [208]. Also psychiatric disorders like depression and anxiety disorders increase the risk for comorbid PTSD. Methods to diagnose PTSD involve measures of symptomatology as can be found in the Clinician-Administered PTSD scale (CAPS), Impact of Events Scale (IES) and PTSD symptoms checklist (PCL).
Neurobiological approaches to understand PTSD are developing [209]. Increased activation of the sympathetic nervous system and hypocortisolism are described as features of autonomic and endocrine dysregulation [210;211]. Indeed, adrenergic activation in the face of low corticosterone has been shown to facilitate learning in animals [212]. Although basal cortisol levels appear to be low, PTSD patients are more sensitive to stress and glucocorticoid negative feedback. However, Baker and colleagues [213;214] have reported increased cortisol, noradrenalin and interleukin 6 in the cerebrospinal fluid, but not in blood plasma of PTSD patients. This shows the complexity of cortisol involvement in PTSD. In addition, the hippocampus has a smaller volume in PTSD patients compared to healthy controls [215;216]. This is often discussed as consequence of high corticosteroid exposure and thus contradicts hypocortisolism, but corresponds to high cortisol levels in cerebrospinal fluid during PTSD.
Often, PTSD is diagnosed together with generalized anxiety disorder, depression or chronic fatigue syndrome [217;218], suggesting that next to stressful live events that contribute to the onset of the disorder there might be common molecular nominators. Indeed, twin studies (like in Vietnam veterans [219]) suggest that genes contribute for an important part in vulnerability to PTSD. Thus, the current point of view is that the risk for PTSD is the product of multiple genes and non-genetic (environmental) factors such as stress [220].
Treatment of PTSD can involve eye movement desensitization and reprocessing therapy or a combination of psychotherapy and medications such as antidepressants and antipsychotic drugs.

Recent clinical trials suggest however that administration of corticosteroids may have a beneficial effect on established PTSD and specific (fear-related) phobia [221-223]. In patients with PTSD, low-dose cortisol treatment for one month reduced symptoms of traumatic memories without causing adverse side effects.

Box 5. PTSD

Post traumatic stress disorder (PTSD)

PTSD is defined as "a normal response to extreme stress resulting in chronic anxiety"[1]. It is characterized by intrusive persistent memories of the trauma, avoidance of stimuli associated with the trauma, numbing of general responsiveness and hyperarousal. Intrusions of a traumatic memory occur as "flashback". Patients avoid social contacts, places and thoughts; have feelings of detachment and an increased risk for drug abuse. Hyperarousal is described as feeling irritable, with problems to concentrate, but also sudden outbursts of anger. Other symptoms include sleep disturbances, including nightmares, insomnia, sleep movement disorders and daytime fatigue. The onset of PTSD follows the trauma with a latency period that may range from a few weeks to months. In a small proportion of cases the condition may follow a chronic course over many years, with eventual transition to an enduring personality change [8;9].

1.7. Scope of the thesis

1.7.1 Objective

Corticosteroids display a large individual variation in effects on emotional processes and cognitive performance. These central effects exerted by the steroids can be facilitating under normal conditions, but become impairing if the action of the stress hormone is excessive, prolonged or inadequate. Such dysregulated corticosteroid action is thought to compromise information processing underlying the proper integration of emotional and cognitive processes which may enhance the vulnerability to stress-related disorders such as depression and PTSD. In this thesis I will focus on the role of the two distinct receptor types that mediate the action of the corticosteroids on specific domains of emotion and cognition, that are considered separately as well as in interaction.

The following questions are addressed:

1. Do corticosteroids affect emotion and cognition via differential MR and GR **activation**? Are emotion and cognition correlated? (chapter 2)

2. Do emotion and cognition correspond to distinct MR, GR **expression** and stress sensitivity as it is expressed in two mouse strains? (chapters 3,4)
3. Does exogenous corticosterone eliminate strain differences in emotion and cognition for a negative event? (chapter 5)
4. Does the time of treatment (before or directly after the negative event) differentially influence memory formation and extinction? (chapter 5)
5. What is the specific function of MR during memory formation and extinction of a stressful emotional experience? (chapter 6)

1.7.2 Experimental approach and outline

In order to study how differential MR and GR activation influences emotion and cognition, plasma corticosterone concentration of C57BL/6J mice was clamped to different levels followed by extensive testing for emotional and cognitive functioning in the modified holeboard. We expected that both emotion and cognition would be affected by variations in corticosterone concentrations, showing a differential and coordinated contribution of MR and GR **(chapter 2)**.
Next we assessed if naturally occurring differences in MR and GR expression would correspond to endocrine and behavioural stress sensitivity, emotional and cognitive functioning. Two inbred mouse strains (BALB/c and C57BL/6J) were characterised for MR and GR protein and mRNA expression in the hippocampus, amygdala and PFC and further tested for emotional and cognitive behavioural patterns in the elevated plus maze and modified holeboard. We expected that BALB/c mice would display glucocorticoid stress system markers indicative for a stress susceptible phenotype; high stress induced corticosterone concentrations and an altered MR/GR balance compared to C57BL/6J mice. In addition, we expected that emotional expressions would differentially contribute to learning and memory in BALB/c and C57BL/6J mice **(chapter 3)**.
These mouse strains (BALB/c and C57BL/6J), which indeed exhibited distinct differences in susceptibility to stress, were subjected to a specifically designed fear conditioning paradigm. We expected that combined, but alternating cue-context exposure would identify either generalized or stimulus-specific fear-responses, and thus determine the influence of the strain-dependent susceptibility to stress on emotion and cognition for an emotionally negative event **(chapter 4)**. In order to assess the impact of corticosteroids on the acquisition and consolidation phase of fear memory BALB/c and C57BL/6J mice were injected with corticosterone directly before or after acquisition of fear conditioning and the retrieval and extinction of context- and cue-related fear memories were observed **(chapter 5)**.
To further specify the role of MR in emotion and cognition, forebrain $MR^{CaMKCre}$ knockout mice were studied for behavioural and corticosterone response,

emotion and cognition in a one trial modified hole board test followed by a fear conditioning paradigm **(chapter 6)**.

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